IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

DAVIDSON et al.

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Title: METHODS OF TRANSDUCING NEURAL CELLS USING LENTIVIRUS VECTORS

DECLARATION OF BEVERLY L. DAVIDSON, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Beverly L. Davidson, hereby declare as follows:

1. I received my Ph.D. in Biological Chemistry form the University of Michigan, Ann Arbor, where I focused my studies on human genetics. I am currently a Professor at the University of Iowa College of Medicine ("the University") and the Vice Chair for Research in the Department of Internal Medicine at the University. I am extremely familiar with the fields of gene therapy and genetic research, having actively worked in these fields for over 20 years. I have authored and coauthored approximately 380 publications in these fields. A copy of my Curriculum Vitae is attached hereto as Exhibit A.

2. I am an inventor of the above-captioned patent application ("the Application").

3. I believe that successful delivery and expression of β-galactosidase is in

fact a predictor that a therapeutic protein could be delivered and expressed with a subsequent therapeutic effect. It was an continues to be routine in the field of gene therapy to first deliver a reporter gene such as β -galactosidase in order to determine whether successful delivery and expression of a therapeutic gene is even feasible. This view is widely accepted in the field of gene therapy. For example, in the study described in Alisky et al., *NeuroReport* (2000) 11:2669-2673, on which I am a coauthor, the lacZ gene was delivered using FIV vectors and the identical system described in the Application. Based on the results using the lacZ gene, we concluded that these vectors showed promise "in correction of cerebellar degeneration both hereditary and acquired." Alisky et al., page 2673. Similarly, in Stein and Davidson, *Meth. Enzymol.* (2002) 346:433-454, we commented on the Alisky study and concluded: "Thus, an FIV vector encoding a therapeutic molecule has potential clinical value." Stein and Davidson, page 448. These statements, published in well-respected peer-reviewed journals, show that scientists in the field of gene therapy indeed rely on studies using reporter genes in order to determine the feasibility of delivering therapeutic proteins. Why? Because it tells us that the virus can infect the target cell, that the machinery in the cell allows for appropriate uncoating of the virus and trafficking of the nucleocapsid to the nucleus, and that the nucleocapsid can enter the nucleus and gene expression can ensue. Using reporters we also get a sense of the longevity of gene expression because when we can no longer 'see' it by whatever means (quantitative PCR, northern blotting, reporter gene assay). 'Seeing' expression indicates gene transcription and is the first criterion for moving forward with a therapeutic transgene in animal models. The fact that 'gene therapy hasn't worked' has nothing to do with this application, but rather investigators mismatching vectors and disease indications. We are now moving more slowly, and more rationally, towards using the right vector for the right disease, and reporter vectors are helping us hone in appropriate applications for the vector under study.

4. There are numerous examples of successful gene delivery and expression with a therapeutic effect following the successful delivery and expression of a reporter gene such as β -galactosidase. For example, Haskell et al., *Gene Therapy* (2000) 10:34-42 used the same FIV delivery system as described in Alisky and in the Application, to successfully deliver and express tripeptidyl peptidase I (TPP-I), in Purkinje cells. TPP-I is the enzyme deficient in classical late-infantile neuronal ceroid lipofuscinosis (LINCL). Similarly, Brooks et al., *Proc. Natl. Acad. Sci. USA* (2002) 99:6216-6221, delivered both the lacZ gene and β -glucuronidase gene to adult β -glucuronidase-deficient mice using the FIV-based vectors described and used in the Application. As explained in the paper, the β-galactosidase gene was first delivered in order to evaluate the feasibility of the FIV system to transduce and ultimately express β -galactosidase in the CNS (see, pages 6218-6219, bridging paragraph). When the β -glucuronidase gene was delivered using the same system, therapeutic benefits were achieved. In fact, established disease was *reversed*, a preclinical study of great importance (see accompanying commentary to this paper on PubMed, appended as Exhibit B). Although Brooks does not pertain to transducing cerebellar neurons *per se*, Brooks shows that the successful use of β-galactosidase can indeed be predictive of the success of subsequent delivery of a therapeutic gene. Scientists in the field of gene therapy, such as myself, are in fact excited by positive results using reporter genes because we believe results using these genes can be reasonably extrapolated to the ability to deliver and express a therapeutic protein.

5. We have also successfully used the lentiviral vector gene delivery system described in the Application to deliver β-glucuronidase to MPS VII mice, and achieve expression of β -glucuronidase in cerebral neurons, using the methods described in the Application. In particular, β-glucuronidase deficiency, like other

mucopolysaccharidoses, results in progressive lysosomal accumulation of glycosaminoglycans, resulting in cell, tissue and organ dysfunction, including mental deterioration. In this study, the scientifically-accepted β-glucuronidase-deficient mouse model was used to examine the ability of a VSVg-pseudotyped FIV vector (as described in the Application) encoding β-glucuronidase (FIV_gluc) to treat the central nervous system (CNS) aspect of this lysosomal storage disease. To evaluate FIV βgluc-mediated CNS transduction and correction of lysosomal distention, β-glucuronidase-deficient mice were given unilateral injections of FIV βgluc, and brains were harvested at 3, 6 and 18 weeks for examination of enzyme activity and cellular pathology. β-glucuronidase activity was evident throughout much of the injected hemisphere at the 3 week time-point (26±6%), and declined only slightly by the 18 week time-point (18±2%). Histological correction of lysosomal storage was observed in the ipsilateral striatum at the 3 week time-point, while at 6 weeks there was substantive storage reduction in both hemispheres of the brain, indicative of β-glucuronidase secretion and of cross-correction of distant cells. The absence of lysosomal inclusions was maintained through the 18-week time-point. To test the potential of FIVβgluc therapy to halt or reverse learning and memory deficits in aged mice, we used the repeated acquisition and performance chamber (RAPC) test. RAPC sessions performed on 8 and 13 week-old mice prior to gene transfer confirmed significant learning deficits in deficient mice (-/-), compared to heterozygous (normal) littermates (+/-). At 15 weeks of age, these mice were given bilateral injections of FIVβgluc and retested in RAPC sessions conducted 3, 4 and 5 weeks later. Marked reversal of learning defects was observed, such that differences were no longer evident between the FIVβgluc-treated -/- mice and +/- controls.

6. The above results indicate (1) that recombinant FIV-based vectors can mediate extensive and persistent transgene expression in mammalian brain, and (2) that

enzyme replacement via gene transfer is capable of reversing severe neurological deficits of mammals with advanced lysosomal storage disease. Based on these results, and the other studies described above, I would expect that lentivirus-mediated gene delivery of therapeutic proteins, such as β-glucuronidase, would also be successful in providing expression in cerebellar neurons with a therapeutic effect. In fact, as explained above, my coworkers and I have shown successful delivery and expression of another therapeutic enzyme, TPP-I, in Purkinje cells, using the vectors and methods described in the Application. See, Haskell et al., *Gene Therapy* (2000) 10:34-42, appended as Exhibit C.

7. Based on the foregoing, it is my opinion that there is every reason to believe that expression of a therapeutic protein in cerrebellar neurons can result in a therapeutic benefit, such as treating or preventing a CNS disorder, and treating or preventing cerebellar degeneration.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Beverly L. Davidson, Ph.D.

June 27, 05
Date

UNIVERSITY OF IOWA COLLEGE OF MEDICINE CURRICULUM VITAE

Beverly L. Davidson, PhD

I. EDUCATIONAL AND PROFESSIONAL HISTORY

A. Institutions Attended

Year	Degree	Institution
1977-81	B.S. (Biology, High Distinction)	Nebraska Wesleyan University, Lincoln, NE
1981-83	M.S. (Graduate Program in Biological Chemistry	University of Michigan, Ann Arbor, MI
1984-87	Ph.D. (Graduate Program in Biological Chemistry	University of Michigan, Ann Arbor, MI

B. Professional and Academic Positions

Year	Position	Institution
1982-83	Research Assistant	University of Nebraska, Lincoln, NE
1988-90	Postdoctoral Fellow	University of Michigan Medical Center, Ann Arbor, MI
1990-92	Research Investigator	University of Michigan Medical Center, Ann Arbor, MI
1992-94	Assistant Research Scientist	University of Michigan Medical Center, Ann Arbor, MI
1993-94	Director	Vector Core, University of Michigan Medical Center, Ann Arbor, MI
1994	Assistant Professor	University of Michigan Medical Center, Ann Arbor, MI
1994-98	Assistant Professor	University of Iowa College of Medicine, Iowa City, IA
1994-	Director	Gene Transfer Vector Core, University of Iowa College of Medicine, Iowa City, IA
1998-01	Associate Professor	University of Iowa College of Medicine, Iowa City, IA
1999-	Roy J Carver Chair	University of Iowa College of Medicine Iowa City, IA
2001-	Professor	University of Iowa College of Medicine, Iowa City, IA
2001-05	Co-Director	Iowa Biosciences Advantage Program
2004--	Vice Chair for Research	Department of Internal Medicine, University of Iowa, Iowa City, IA

C. Honors, Awards, Recognitions

Year	Award
1977-81	Presidents Scholarship Award, Nebraska Wesleyan University, Lincoln, NE
1979	Beta Beta Beta Biology Honorary Society, Nebraska Wesleyan University, Lincoln, NE
1980	Phi Kappa Phi Honor Society, Nebraska Wesleyan University, Lincoln, NE
1988	VI International Symposium on Human Purine and Pyrimidine Metabolism Scholarship Award
1988-90	Fellowship for Protein Structure and Design, University of Michigan, Ann Arbor, MI
1990-93	National Arthritis Foundation Postdoctoral Fellow Award

1993	Mentor for Steve Doran, MD – recipient, Residents Award, Congress of Neurological Surgeons
1993	Co-mentor for John Hartman, recipient, Abraham H. Grant Scholastic Award and American College of Rheumatology Medical Student Achievement Award
1994-95	Mentor for Troy J. Plumb – recipient, Howard Hughes Medical Institute Research Training Fellowship for Medical Students
1995	Mentor for Troy J. Plumb – recipient, AFCR/CSCR Trainee Investigator Award
1995	Mentor for Troy J. Plumb – recipient, AFCR Medical Student Award
1996	Mentor for Steven Beer – recipient, University of Iowa Resident's Research Award, Department of Surgery
1996	Mentor for Francis Miller – recipient, K08 Award
1997	Mentor for Francis Miller – recipient, Young Investigator Award
1997	Mentor for Camilla Bowman Matthews, - recipient, AHA Medical Student Research Award
1998	Mentor for Ronald E. Haskell – recipient, Battens Disease Support & Research Association grant
1998	Mentor for Haibin Xia – recipient, American Heart Association grant
1998	Mentor for Lane Law – recipient, American Society of Gene Therapy Travel Award
1999	Roy J Carver Endowed Chair
2000	Mentor for Inês Martins – recipient, University of Iowa College of Medicine Research Week award
2000	Mentor for Stephanie M. Hughes – recipient, University of Iowa College of Medicine Research Week award
2000	Mentor for Colleen S. Stein – recipient, University of Iowa College of Medicine Research Week award
2000	Mentor for Joseph Alisky – recipient, Amyotrophic Lateral Sclerosis Association Research Grant
2000	Mentor for Qinwen Mao – recipient, University of Iowa Biosciences Initiative award
2000	Mentor for Joseph Alisky – Invited Speaker, American Society of Gene Therapy meeting
2000	Mentor for Colleen S. Stein – Invited Speaker, American Society of Gene Therapy meeting
2000	Mentor for Stephanie M. Hughes – Invited Speaker, American Society of Gene Therapy meeting
2000	Mentor for Jason A. Heth – recipient, NIH Fellowship grant
2000	Mentor for Colleen S. Stein – recipient, NIH/CFF Pilot Grant
2000	Mentor for Stephanie M. Hughes – recipient, Battens Disease Support & Research Association Grant
2001	Mentor for Jason A. Heth – recipient, American Society of Gene Therapy Outstanding Research Award for Postdoctoral Fellows
2001	Mentor for Jason A. Heth – recipient, American Society of Gene Therapy Travel Award
2001	Mentor for Jason A. Heth – Invited Speaker, American Society of Gene Therapy
2001	Mentor for Joseph M. Alisky – Invited Speaker, American Society of Gene Therapy
2001	Mentor for Haibin Xia – Invited Speaker, American Society of Gene Therapy
2002	Mentor for Gumei Liu – Invited Speaker, American Society of Gene Therapy
2002	Mentor for Adam Espie-Ziemann, Award Winner, University of Iowa Medical Student Research Day
2003	Mentor for Scott Q Harper, Award Winner, University of Iowa College of Medicine Research Week
2003	Mentor for Henry L. Paulson, Award Winner, Paul Beeson Physician Faculty Scholars in Aging Research Award
2005	Mentor for Scott Q Harper, Best Basic Science Poster Award Winner, Department of Internal Medicine Research Day, March 2005.
2005	Mentor for Gumei Liu, Best Pre-doctoral Trainee Poster Award Winner, Department of Internal Medicine Research Day, March 2005.

II. TEACHING

A. Teaching Assignments

Year	Course Title	Wks/Yr	Hrs/Yr
1994--	Pulmonary Fellows Research, University of Iowa, Iowa City, IA		
1995-96	Molecular Biology Program, Student Seminar Series, University of Iowa, Iowa City, IA	38	100
1997--	Medical Students Training Program Cttee		
1997--00	Lecturer, Cancer Biology Program, University of Iowa, Iowa City, IA	2	8
1997-98	Lecturer, Neuroscience Program, University of Iowa, Iowa City, IA	38	100
1997–00	Lecturer, Genetic Analysis of Biological Systems, University of Iowa, Iowa City, IA	2	8
1998–00	Lecturer, Cancer Biology Program, University of Iowa, Iowa City, IA	2	8
1998--	Gene Therapy Research Group	38	50
1999--	Lecturer, Mini Medical School, University of Iowa, Iowa City, IA	1	2
1999	Lecturer, Mucopolysaccharidosis and Related Diseases Symposium, University of Minnesota	1	2
1999--	Iowa Biosciences Initiative Committee		
2000	Lecturer, Undergraduate Biotechnology Program, University of Puerto Rico	1	17
2000	Lecturer, Mucopolysaccharidosis and Related Diseases Symposium, University of Minnesota	1	2
2000	Lecturer, University of Iowa Nursing Conference on "Genetics in Oncology Nursing: New Dimensions in Advanced Practice" – Gene Therapy: What's Ahead	1	2
2000	Lecturer, University of Iowa Mini Symposium – Genetics and the Internist	1	2
2000	Lecturer, University of Iowa Summer Seminar Series for Undergraduate Research Students	1	2
2000	Facilitator: Principles of Molecular and Cell Biology	5	5
2000--	Lecturer, University of Iowa "Genetic analysis of biological systems" course	1	2
2001	Lecturer, University of Iowa "Experimental approaches to Human Disease: The Functional Genomics Era"	2	6
2002	Lecturer, Principles in Molecular & Cell Biology course, University of Iowa	3	3
2002	Lecturer, Genetics Analysis course, University of Iowa	2	3
2002	Lecturer, Methods in Neuroscience course, University of Iowa	1	2
2002	Lecturer, Functional Genomics course, University of Iowa	2	3
2002	Lecturer, Biosciences undergraduate seminar, University of Iowa	1	1
2002	Lecturer, Microbiology undergraduate seminar, University of Iowa	1	1
2002	Lecturer, Topics in Molecular Biology course, University of Iowa	1	2
2002	Lecturer, MSTP Conversations in Research, University of Iowa	1	2
2002	Lecturer, ABC's of Gene Therapy seminar, University of Iowa	1	2

2003	Lecturer, Principles in Molecular and Cellular Biology, University of Iowa	4	4
2003	Lecturer, Genetic Analysis, University of Iowa	2	4
2004	Lecturer, Human Physiology for Pharmacy Students, University of Iowa	1	2
2004	Lecturer, Intermediate Physiology, University of Iowa	1	2
2004	Lecturer, Human Physiology for Biomedical Engineering students, University of Iowa	1	2
2004	Lecturer, Developmental Neurobiology, University of Iowa	1	2
2005	Lecturer, Human Physiology, University of Iowa	3	4

B. Staff/Students Supervised

B.1 Students

Year	Student
1994–95	Troy Plumb (HHMI Pre-doctoral Fellowship)
1996–97	Camilla Matthews, BS (Iowa Heart Pre-doctoral Trainee Award)
1997-03	Lane Law (Genetics; Cardiovascular Pre-doctoral Fellowship)
1997--	Yueming Ding, Molecular Biology Program – Thesis Committee
1997-00	Gregory Wu, Neuroscience Training Program – Thesis Committee
1997-98	Laura Rubsam, University of Michigan – Thesis Committee
1997-98	Karl Swanson, Molecular Biology Program – Thesis Committee
1998-99	Brian Foster (MSTP; Molecular Biology)
1998-01	Julie Jacobs, Neuroscience Training Program – Thesis Committee
1998-01	Lisa Busch, Molecular Biology Program – Thesis Committee
1998-00	Ernie Lamb, Radiation Biology Program – Thesis Committee
1999-01	Branimir Cvetkovic, Molecular Biology program – Thesis Committee
1999--	Emily Kuhn, Genetics Program – Thesis Committee
1999-01	McKenzie Hilfers, Neuroscience Program – Thesis Committee
1999--	Sarah Shoesmith, Neuroscience Program – Thesis Committee
1999-00	Eian Murphy, Molecular Biology Program – Thesis Committee
1999-01	Chun Cheng, Molecular Biology Program - Thesis Committee
2000-01	Shana Lippert, Microbiology Program – Thesis Committee
2000--	Laura Norwood, Genetics Program – Thesis Committee
2001--	Gumei Liu, Neuroscience PhD Program - Advisor
2002--	Mee Kyoung Kim, Department of Chemistry – Thesis Committee
2002--	Glen Borchert, Genetics PhD Program - Advisor
2002--	Ben Darbro, Thesis Committee
2002--	Ryan Boudreau, Physiology and Biophysics PhD Program - Adviser
2002--	Sarah Fineberg, MSTP
2003	Emily Peddle, McMaster Co-operative Exchange Program
2003	Sanjay Anandaram, McMaster Co-operative Exchange Program
2003--	Michael Chang, MSTP Program - Adviser
2003--	Julieann Grant – PhD Thesis Committee
2003--	Jenny Bartlett, Genetics – PhD Thesis Committee
2003--	Annie Chaing, Electrical and Computer Engineering – Masters Thesis Committee
2003--	Rebecca van Oosten, Immunology PhD program – Thesis Committee
2003--	Douglas Dylla, PhD Thesis Committee

B.2 Postdoctoral and Others

B.2.i Past

Year	Person
1995-97	Assumpcio Bosch, PhD
1995-97	Steve Beer, MD (Neurosurgery Fellowship)
1997-98	Gongyu Yang, PhD (Cardiovascular Postdoctoral Fellowship)

1997-99	Abdi Ghodsi, MD (Neurosurgery Fellowship)
1997-99	Vladimir Slepushkin, PhD
1997-01	Francis Miller, MD
1999-01	Jason Heth, MD
1995-01	Ronald E. Haskell, PhD
1995-01	Richard D. Anderson, BS, BSMT
1999-02	Stephanie M. Hughes, PhD
1999-02	Joseph Alisky, MD, PhD
2000-02	Grace Shih-yi Yang, MD

B.2.ii *Present*

Year	Person
1995--	Colleen S. Stein, PhD
1995--	Patrick Staber, BS
1997--	Haibin Xia, PhD
1998--	Qinwen Mao, PhD
2001--	Rajeev Vibhakar, MD, PhD, MPH
2001--	Xiaohua He, PhD
2002--	Yong Hong Chen, PhD
2002--	Scott Q. Harper, PhD

C. Other Contributions (See also Section II.A)

Year	Contribution
1996--	Virology Journal Club
1996--	Neuroscience Seminar
1996--	Physiology Workshop
1996--	Molecular Biology Workshop
1996--	Pulmonary Conference
1998--	Levitt Journal Club
2001--	Neurology Grand Rounds

III. SCHOLARSHIP

A. Publications

Peer Reviewed Papers

1. **Davidson BL,** Boernke WE. Amphibian ornithine aminotransferase: Some general biological and chemical characteristics. Comp Biochem Physiol 72B:469-471, 1982.
2. Dadonna PE, Mitchell BS, Meuwissen HJ, **Davidson BL,** Wilson JM, Koller CA. Adenosine deaminase deficiency with normal immune function. An acidic mutation. J Clin Invest 72:483-492, 1983.
3. Dadonna PE, **Davidson BL,** Perignon JL, Kelley WN. Genetic expression in partial adenosine deaminase deficiency mRNA levels and protein turnover for the enzyme variations in human B-lymphoblast cell lines. J Biol Chem 260:3875-3880, 1985.
4. Wilson JM, Stout JT, Palella TD, **Davidson BL,** Kelley WN, Caskey CT. A molecular survey of hypoxanthine-guanine phosphoribosyltransferase deficiency in man. J Clin Invest 77(1):188-195, 1986.
5. Jensen SG, **Davidson BL,** Seip L. Size variation among proteins induced by sugarcane mosaic viruses in plant tissues. Phytopath 76:528-532, 1986.
6. **Davidson BL**. The genetic basis of hypoxanthine-guanine phosphoribosyltransferase deficiency states in humans. Doctoral dissertation. Horace Rackham School of Graduate Studies, University of Michigan, 1988.

7. **Davidson BL,** Pashmforoush M, Kelley WN, Palella TD. Genetic basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in a patient with the Lesch-Nyhan syndrome ($HPRT_{Flint}$). Gene 63:331-336, 1988.
8. **Davidson BL,** Palella TD, Kelley WN. Human hypoxanthine guanine phosphoribosyl-transferase: A single nucleotide substitution in cDNA clones isolated from a patient with Lesch-Nyhan syndrome ($HPRT_{Midland}$). Gene 68:85-91, 1988.
9. Fujimori S, Hidaka Y, **Davidson BL,** Palella TD, Kelley WN. Identification of a single nucleotide change in a mutant for hypoxanthine-guanine phosphoribosyltransferase gene ($HPRT_{Ann\ Arbor}$). Hum Genet 79:39-43, 1988.
10. **Davidson BL,** Chen S-J, Wilson JM, Kelley WN, Palella TD. Hypoxanthine-guanine phosphoribosyltransferase. Genetic evidence for identical mutations in two partially deficient subjects. J Clin Invest 82(6):2164-2167, 1988.
11. **Davidson BL,** Pashmforoush M, Kelley WN, Palella TD. Human hypoxanthine-guanine phosphoribosyltransferase deficiency: The molecular defect in a patient with gout ($HPRT_{Ashville}$). J Biol Chem 264:520-525, 1989.
12. Fujimori S, **Davidson BL,** Kelley WN, Palella TD. Identification of a single nucleotide change in the hypoxanthine-guanine phosphoribosyltransferase gene ($HPRT_{Yale}$) responsible for Lesch-Nyhan syndrome. J Clin Invest 83(1):11-13, 1989.
13. **Davidson BL,** Tarle SA, Palella TD, Kelley WN. Molecular basis of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency in ten subjects determined by direct sequencing of amplified transcripts. J Clin Invest 84:342-346, 1989.
14. **Davidson BL,** Tarle SA, Van Antwerp ME, Gibbs DA, Watts RE, Kelley WN, Palella TD. Identification of seventeen independent mutations responsible for human hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Am J Hum Genet 48(5):951-958, 1991.
15. Tarle SA, **Davidson BL,** Wu VC, Zidar FJ, Seegmiller JE, Kelley WN, Palella TD. Determination of the mutations responsible for the Lesch-Nyhan syndrome in seventeen subjects. Genomics 10:499-501, 1991.
16. **Davidson BL,** Roessler BJ and Palella TD: Expression of normal and variant human hypoxanthine-guanine phosphoribosyltransferase in E. coli. Adv Exp Med Biol 309B:105-108, 1991.
17. **Davidson BL,** Brown JE, Weber CH, Palella TD, Roessler BJ. Synthesis of normal and variant human hypoxanthine-guanine phosphoribosyltransferase in *Escherichia coli.* Gene 123:271-275, 1993.
18. **Davidson BL,** Allen ED, Kozarsky KF, Wilson JM, Roessler BJ. A model system for *In vivo* gene transfer to the central nervous system using an adenoviral vector. Nat Genet 3:219-223, 1993.
19. Roessler BJ, Allen ED, Wilson JM, Hartman JW, **Davidson BL.** Adenoviral mediated gene transfer to rabbit synovium *In vivo.* J Clin Invest 92:1085-1092, 1993.
20. **Davidson BL,** Doran SE, Shewach DS, Latta JM, Hartman JW, Roessler BJ. Expression of *Escherichia coli* ß-galactosidase and rat HPRT in the CNS of *Macaca mulatta* following adenoviral mediated gene transfer. Exp Neurol 125:258-267, 1994.
21. **Davidson BL,** Golovoy N, Roessler BJ. A 13 base pair deletion in exon 1 of $HPRT_{Illinois}$ forms a functional GUG initiation codon. Hum Genet 93(3):300-304, 1994.
22. Roessler BJ, **Davidson BL.** Direct plasmid mediated transfection of adult murine brain cells *In vivo* using cationic liposomes. Neurosci Lett 167(1-2):5-10, 1994.
23. Li T, Adamian M, Roof DJ, Berson EL, Dryja TP, Roessler BJ, **Davidson BL.** *In vivo* transfer of a reporter gene to the retina mediated by an adenoviral vector. Invest Ophthalmol Vis Sci 35(5):2543-2549, 1994.

24. Smythe WR, Hwang HC, Amin KM, Eck SL, **Davidson BL,** Wilson JM, Kaiser LR, Albelda SM. Use of recombinant adenovirus to transfer the herpes simplex virus thymidine kinase (HSV*tk*) gene to thoracic neoplasms: An effective in vitro drug sensitization system. Cancer Res 54(8):2055-2059, 1994.
25. Shewach DS, Zerbe LK, Hughes TL, Roessler BJ, Breakefield XO, **Davidson BL.** Enhanced cytotoxicity of antiviral drugs mediated by adenoviral directed transfer of the herpes simplex virus thymidine kinase gene in rat glioma cells. Cancer Gene Ther 1(2):107-112, 1994.
26. Doran SE, Ren XD, Betz AL, Pagel MA, Neuwelt EA, Roessler BJ, **Davidson BL.** Gene expression from recombinant viral vectors in the CNS following blood-brain barrier disruption. Neurosurgery 36(5): 965-970, 1995.
27. Roessler BJ, Hartman JW, Latta JM, Janich S, **Davidson BL.** Inhibition of IL-1 induced effects in synoviocytes transduced with the human IL-1 receptor antagonist cDNA using an adenoviral vector. Hum Gene Ther 6:307-316, 1995.
28. Smythe WR, Hwang HC, Elshami AA, Amin KM, Eck SL, **Davidson BL,** Wilson JM, Kaiser LR, Albelda SM. Treatment of experimental human mesothelioma using adenovirus transfer of the herpes simplex thymidine kinase gene. Ann Surg 222(1): 78-86, 1995.
29. Betz AL, Yang G-Y and **Davidson BL.** Attenuation of stroke size in rats using an adenoviral vector to induce overexpression of interleukin-1 receptor antagonist in brain. J Cereb Blood Flow Metab 15:547-551, 1995.
30. McCoy RD, **Davidson BL,** Roessler BJ, Huffnagle GB, Simon RH. Expression of human interleukin-1 receptor antagonist in mouse lungs using a recombinant adenovirus: Effects on vector-induced inflammation. Gene Ther 2(7):437-442, 1995.
31. Ooboshi H, Welsh MJ, Rios CD, **Davidson BL,** Heistad DD. Adenovirus-mediated gene transfer *in vivo* to cerebral blood vessels and perivascular tissue. Circ Res 77:7-13, 1995.
32. Li T and **Davidson BL.** Phenotype correction of retinal pigment epithelium in murine mucopolysaccharidosis VII by adenovirus-mediated gene transfer. Proc Natl Acad Sci USA, 92:7700-7704, 1995.
33. Ross BD, Kim B, **Davidson BL.** Assessment of ganciclovir toxicity to experimental intracranial gliomas following recombinant adenoviral-mediated transfer of the herpes simplex virus thymidine kinase gene by magnetic resonance imaging and proton magnetic resonance spectroscopy. Clin Cancer Res 1:651-657, 1995.
34. Chen SJ, Wilson JM, Vallance DK, Hartman JW, **Davidson BL,** Roessler BJ. A recombinant adenoviral vector expressing a soluble form of VCAM-1 inhibits VCAM-1/VLA-4 adhesion in transduced synoviocytes. Gene Ther 2: 469-480, 1995.
35. Nilaver G, Muldoon LL, Kroll RA, Pagel MA, Breakefield XO, **Davidson BL,** Neuwelt EA. Delivery of herpesvirus and adenovirus to nude rat intracerebral tumors following osmotic blood-brain barrier disruption. Proc Natl Acad Sci USA, 92:9829-9833, 1995.
36. McCoy RD, **Davidson BL,** Roessler BJ, Huffnagle GB, Janich SL, Laing TJ, Simon RH. Pulmonary inflammation induced by incomplete or inactivated adenoviral particles. Hum Gene Ther 6:1553-1560, 1995.
37. Muldoon LL, Nilaver G, Kroll RA, Pagel MA, Breakefield XO, Chiocca EA, **Davidson BL,** Weissleder R, Neuwelt EA. Comparison of intracerebral innoculation of osmotic blood-brain barrier disruption for delivery of adenovirus, herpesvirus, and iron oxide particles to normal rat brain. Am J Pathol 147(6):1840-1851, 1995
38. Rios CD, Ooboshi H, Piegors D, **Davidson BL,** Heistad DD. Adenovirus-mediated gene transfer to normal and atherosclerotic arteries: A novel approach. ATVB 15:2241-2245, 1995.

39. Goebel EA, **Davidson BL,** Graham SM, Zabner J, Kern JA. Adenovirus-mediated gene therapy for head and neck squamous cell carcinomas. Ann Otol Rhinol Laryngol 105(7):562-567, 1996.
40. Freese A, During MJ, **Davidson BL,** Gennarelli TA, Kaplitt MG, Flamm ES, Snyder PJ. Transfection of Human Lactotroph Adenoma Cells with an Adenovirus Vector Expressing Tyrosine Hydroxylase Decreases Prolactin Release. J Clin Endocrinol Metab 81(6):2401-2404, 1996.
41. Fang J, Zhu Y-Y, Smiley E, Bonadio J, Rouleau JP, Goldstein SA, McCauley LK, **Davidson BL,** Roessler BJ. Stimulation of new bone formation by direct transfer of osteogenic plasmid genes. Proc Natl Acad Sci USA, 93:5753-5758, 1996.
42. Hagan P, Barks JDE, Yabut M, **Davidson BL,** Roessler BJ, Silverstein FS. Adenovirus-mediated over-expression of interleukin-1 receptor antagonist reduces susceptibility to excitotoxic brain injury in perinatal rats. Neurosci 75(4):1033-1045, 1996.
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130. Ghodsi A, Yang G, Derksen T, Stein C, Anderson RD, Traynelis VC, **Davidson BL**. Extensive ß-glucuronidase activity in murine CNS after adenovirus mediated gene transfer to brain. Soc Neuroscience, November 1998.
131. Vasquez EC, Beltz TG, Johnson RF, Meyrelles SS, **Davidson BL**, Johnson AK. Adenovirus-mediated gene transfer to cells of the hypothalamic-neurohypophyseal tract. Soc. Neuroscience, November 1998.
132. Miller FJ, Mozena J, Foresman EL, Gutterman DD, **Davidson BL**. Superoxide Production is Increased Throughout the Vascular Wall of Atherosclerotic Mice Aorta and Mediated by a Membrane Bound NAD (P) H Oxidase. American Heart Association, November 1998
133. Miller FJ, Mozena JE, Foresman EL, **Davidson BL**, Gutterman DD. Smooth Muscle Cell Production of Superoxide is Increased in Atherosclerosis. American Heart Association, November 1998.
134. Toyoda K, Faraci FM, Russo AF, **Davidson BL**, Heistad DD. Gene transfer of calcitonin gene-related peptide alters reactivity of cerebral arteries. 24th American Heart Association International Conference on Stroke and Cerebral Circulation, Nashville, Tn, February 1999.
135. Vasquez EC, Beltz TG, Johnson RF, Meyrelles SS, **Davidson BL**, Johnson AK. Approaches for Gene Delivery to the Magnocellular-Hypothalamic-Neurohypophyseal System in Rats and Mice. Experimental Biology '99.
136. Belasco KT, Heistad DD, Bishop J, Durham P, Faraci FM, **Davidson BL**, Russo AF. Experimental Biology '99.
137. Kozlowski DA, Redmond DE Jr, Connor B, **Davidson BL**, Bohn MC. Glial cell line-derived neurotrophic factor (GDNF) expression in the caudate and substantia nigra of the African green monkey following gene transfer. 6th Annual Conference,American Society for Neural Transplantation and Repair, Clearwater, Florida, April 29 - May 2, 1999.
138. Toyoda K, Faraci FM, Russo AF, **Davidson BL**, Heistad DD. Gene Transfer of Calcitonin Gene-Related Peptide Alters Reactivity of Cerebral Arteries. Stroke 30(1), 1999.
139. Conner B, Kozlowski DA, Schallert T, Tillerson JL, **Davidson BL**, Bohn MC. Adenoviral vector mediated delivery of Glial Cell line-Derived Neurotrphic Factor (GDNF) provides neuroprotection in the aged Parkinsonian rat. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
140. Wang G, Slepushkin V, Deering C, Shao J, Bodner M, Jolly DJ, **Davidson BL**, McCray PB Jr. Calcium Chelation Enhances Gene Transfer to Differentiated Airway Epithelia by Opening Tight Junctions. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
141. Ghodsi A, Stein CS, Derksen TA, Johnson JC, Sauter SL, Jolly DJ, Martins I, **Davidson BL**. FIV-Mediated Gene Transfer to the CNS and Liver of ß-Glucuronidase Deficient Mice. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
142. Derksen TA, Johnson JC, Sauter SL, Jolly DJ, **Davidson BL**. Correction of the RPE Defect in ß-Glucuronidase Deficient Mice with Recombinant FIV-Based Vectors. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
143. Xia H, Anderson B, Anderson RD, **Davidson BL**. A Step Towards Global Delivery of Recombinant Adenovirus Vectors to Brain Microvasculature: Using Transferrin Receptor Targeted Adenovirus to Target the Brain Microcapillary Endothelium. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
144. Slepushkin VA, Staber PD, **Davidson BL**. Use of Adenovirus Vectors for Efficient Expression of Foreign Envelope Proteins for Production of Pseudotyped Retroviruses. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
145. Stein, CS, Martins I, **Davidson BL**. Sustained Reduction in Plasma Cholesterol in LDL Receptor Deficient Mice After Recombinant Adenovirus Gene Therapy Combined with

Anti-CD40 Ligand-Induced Immunosuppression. American Society of Gene Therapy, Washington DC, June 9-13, 1999.

146. Ghodsi A, Stein CS, Derksen TA, Martins I, Anderson RD, **Davidson BL**. Systemic Hyperosmolality Improves ß-Glucuronidase Distribution and Pathology in the MPS VII Brain Following Intraventricular Gene Transfer. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
147. Wang G, Slepushkin V, Zabner J, Johnston J, Sauter S, Jolly DJ, **Davidson BL**. Feline Immunodeficiency Virus (FIV) Vectors Transduce Non-Dividing Human Airway Epithelia. American Society of Gene Therapy, Washington DC, June 9-13, 1999.
148. Slepushkin, VA, Staber PD, **Davidson BL**. Influenza virus infection of cultured primary human airway cells. Am Soc Virol. Amherst, MA July 10-14, 1999.
149. Kozlowski DA, Conner B, Tillerson JL, Schallert T, **Davidson BL**, Bohn MC. CDNF gene delivery after 6-OHDA induced degeneration rescues dopaminergic (DA) neurons, maintains striatal projections and ameliorates behavioral deficits. Soc Neuroscience, Miami Beach, FL October 23-28, 1999.
150. Haskell RE, Pearce DA, **Davidson BL**. Effects of Point Mutations on the Intracellular Trafficking of the Juvenile Neuronal Ceroid Lipofuscinosis Protein CLN3. Soc Neuroscience, Miami Beach, FL, October 23-28, 1999.
151. Haskell RE, Hughes SM, Anderson RD, Alisky JM, Stocker CM, **Davidson BL**. Different patterns of secretion and uptake of soluble lysosomal enzymes after gene transfer to the CNS: implications for therapy. American Society of Gene Therapy, Denver, CO, May-June, 2000.
152. **Davidson BL**, Brooks AI, Stein CS, Heth JA, Dubensky TW, Sauter SL, Cory-Slechta DA, Federoff HJ. Correction of cellular pathology and behavioral deficits in adult ß-glucuronidase-deficient mice after FIV vector-mediated gene transfer to brain. American Society of Gene Therapy, Denver, CO, May-June, 2000.
153. Stein CS, **Davidson BL**, Heth JA, Martins I, Kotin RM, Derksen TA, Ghodsi A, Chiorini JA. CNS transduction by AAV type 2, 4 and 5 vectors. American Society of Gene Therapy, Denver, CO, May-June, 2000.
154. Alisky JM, Hughes SM, Dubensky TW, Sauter SL, Staber PD, Chiorini JA, **Davidson BL**. Recombinant FIV and AAV5 vectors efficiently transfect cerebellar neurons. American Society of Gene Therapy, Denver, CO, May-June, 2000.
155. Heth JA, Stein SC, Chiorini JA, Martins I, Derksen TA, **Davidson BL**. The effects of systemic hyperosmolality on recombinant AAV4- and AAV5-mediated gene transfer following intraventricular injection. American Society of Gene Therapy, Denver, CO, May-June, 2000.
156. Derksen TA, Ghodsi A, Redmond DE, Dubensky TW, Sauter SL, Townsend K, Sheridan PL, **Davidson BL**. Gene delivery to primate brain using recombinant FIV-based vectors. American Society of Gene Therapy, Denver, CO, May-June, 2000.
157. Anderson RD, Haskell RE, Xia H, Scheel M, Roessler BJ, **Davidson BL**. The rapid generation of recombinant adenovirus vectors using simple methods. American Society of Gene Therapy, Denver, CO, May-June, 2000.
158. Xia H, Anderson RD, Mao Q, **Davidson BL**. Novel shuttles for the rapid generation of adenovirus vectors that express transgenes in E1 and E3. American Society of Gene Therapy, Denver, CO, May-June, 2000.
159. Hughes SM, Toro R, Derksen TA, Staber PD, Dubensky TW, Sauter SL, **Davidson BL**. Primary neural progenitor cells: the effects of FIV-mediated transduction on differentiation in vitro and in vivo. American Society of Gene Therapy, Denver, CO, May-June, 2000.
160. Martins I, Stein CS, Miller FJ, **Davidson BL**. Gene therapy with recombinant adenovirus encoding the low density lipoprotein receptor (AdLDLR) protects against atherosclerosis in LDLR-deficient mice. American Society of Gene Therapy, Denver, CO, May-June, 2000.
161. Zabner J, Seiler M, Walters R, Kotin RM, **Davidson BL**, Fulgeras W, Chiorini JA. AAV5 but not AAV2 bind to the apical surface of airway ep8ithelia and facilitate gene transfer. American Society of Gene Therapy, Denver, CO, May-June, 2000.
162. Haskell RE, Hughes SM, Anderson RD, Alisky JM, Stocker CM, Sohar I, Lobel P, **Davidson BL**. Gene therapy approaches for CLN2. The Eighth International Congress on Neuronal-Ceroid Lipofuscinoses, NCL-2000, Oxford, England, September 20-24, 2000.
163. Hughes SM, Toro R Jr, Anderson RD, Haskell RE, Staber PD, Sauter SL, Dubensky TW Jr, Jolly DJ, **Davidson BL**. Neural progenitor cell therapy for the neuronal ceroid

lipofuscinoses. The Eighth International Congress on Neuronal-Ceroid Lipofuscinoses, NCL-2000, Oxford, England, September 20-24, 2000.

164. Stein CS, Brooks AI, Heth JA, Dubensky TW Jr, Sauter SL, Townsend K, Cory-Slechta DA, Howard MA, Federoff HJ, **Davidson BL**. Correction of cellular pathology and behavioral deficits in adult ß-glucuronidase-deficient mice after FIV vector-mediated gene transfer to murine brain. Society for Neuroscience, New Orleans, November 4-8, 2000.
165. Hughes SM, Haskell RE, **Davidson BL**. Gene and cell replacement in neurodegenerative lysosomal storage diseases. ComBio 2000, Wellington, New Zealand, December 11-14, 2000.
166. Sinn PL, Wang G, Nosakowski JA, Staber P, Sauter S, Dubensky TW Jr, Jolly D, Sanders DA, **Davidson BL**, McCray PB Jr. Pseudotyping feline immunodeficiency virus (FIV)-based vectors to target the apical surface of differentiated human airway epithelia. North American Cystic Fibrosis Conference, Baltimore, MD November 9-12, 2000.
167. Scott JJ, Wang G, **Davidson BL**, McCray PB Jr. Formulation of adenoviral vectors with agents that modify epithelial junctions enhances gene transfer to human airway epithelia. North American Cystic Fibrosis Conference, Baltimore, MD November 9-12, 2000.
168. Wang G, Xia H, **Davidson BL**, McCray PB Jr. Effects of epithelial differentiation and Pit2 receptor, localization on gene transfer with retroviral vectors pseudotyped with the amphotropic envelope glycoprotein. North American Cystic Fibrosis Conference, Baltimore, MD November 9-12, 2000.
169. Hughes SM, Haskell RE, **Davidson BL**. Gene and cell replacement in neurodegenerative lysosomal storage diseases. ComBio 2000, Wellington, New Zealand, December 11-14, 2000.
170. Russell SR, Lotery AJ, Derksen TA, **Davidson BL**, Stone EM. A manual, remotely actuated injector for sub-retinal gene therapy in non-human primates. Association for Research in Vision and Opthalmology, Ft Lauderdale, FL, April 29 – May 4, 2001.
171. Lotery AJ, Derksen TA, Mullins RF, Kopp KK, Rosenow JR, Stone EM, **Davidson BL**, Sauter S, Russell SR. Evaluation of lentiviral vectors as possible agents for gene therapy to the neurosensory retina in a non-human primate model. Association for Research in Vision and Opthalmology, Ft Lauderdale, FL, April 29 – May 4, 2001.
172. Yang G, Derksen TA, Schmidt M, Kotin RM, **Davidson BL**. Transgene expression in photoreceptors of neural retina mediated by adeno-associated virus type 5. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
173. Hughes SM, Brooks AI, Yang G, Slevin M, Haskell RE, Staber PD, **Davidson BL.** FIV-mediated delivery of differentiation factors to mouse eural progenitor cells. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
174. Alisky J, Xia H, Hughes SM, **Davidson BL**. New strategies for brainstem gene therapy. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
175. Law L, **Davidson BL**. The Ad5 receptor is not the Ad30 receptor. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
176. Heth JA, Kasperski J, **Davidson BL**. Pseudotyping feline immunodeficiency virus with the Ross River virus envelope protein directs transgene expression in astrocytes. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
177. Derksen TA, Lotery AJ, Russell SR, Chiorini JA, Schmidt M, Stone EM, **Davidson BL**. Evaluation of AAV2, AAV4, and AAV5 for gene therapy to the retina of the non-human primate. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
178. Heth JA, Martins IH, Chen J, Chiorini JA, Derksen TA, Hoshi T, **Davidson BL**. AAV5-mediated gene transfer corrects hippocampal learning defects in murine MPS VIII. Presented at the 4th annual meeting of the Society of Gene Therapy, Seattle, WA, May-June, 2001.
179. Hughes SM, Brooks AI, Yang GS, Haskell RE, Fellows RE, Staber PD, **Davidson BL**. FIV-mediated delivery of differentiation factors to mouse neural stem cells. Society for Neuroscience, San Diego, November 10-15, 2001.
180. Xia H, Alisky JM, Mao Q, Coulter JD, **Davidson BL**. PTD-modified proteins expressed from viral vectors improves CNS distribution. Society for Neuroscience, San Diego, November 10-15, 2001.

181. Yang GS, Derksen TA, Schmidt M, Howard M, Kotin RM, **Davidson BL**. Transgene expression in photoreceptors of neural retina mediated by adeno-associated virus type 2 and type 5. Society for Neuroscience, San Diego, November 10-15, 2001.
182. Mao Q, **Davidson BL**. Development expression of CLN3 in the mouse nervous system. Soceity for Neuroscience, San Diego, November 10-15, 2001.
183. Navalitloha Y, Anderson R, **Davidson BL**, Harrod C, Xe H, Bohn MC. Expression of green fluorescent protein (GFP) in brain from a self-regulating adenovral (Ad) vector is shut off by doxycycline (DOX). Society for Neuroscience, San Diego, November 10-15, 2001.
184. Sinnay P, Lindley TE, Staber PD, Cassell MD, **Davidson BL**, Davisson RL. Selective cre-mediated gene deletion in key cardiovascular regions of the brain: comparison of two viral delivery systems. American Heart Association, 55th Annual Fall Conference, 2001.
185. SM Hughes, AI Brooks, F Moussavi-Harami, PD Staber, SL Sauter, **BL Davidson**. Viral mediated delivery of differentiation factors to neural progenitor cells. Joint meeting of Australian Neuroscience Society/International Society of Developmental Neuroscience, Sydney, Australia, Jan 31 – Feb 6, 2002.
186. GS Yang, J Lindbloom, Z Yan, J Engelhardt, M Schmidt, R Kotin, **BL Davidson**. Viral mediated transduction of murine retina with AAV2 and 5. The Association for Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL May 5-10, 2002.
187. Q Mao, M Gerety, MK Kim, DF Wiemer, **BL Davidson**. A highly sensitive method for the *in situ* detection of tripeptidyl aminopeptidase I (CLN2). 5th Annual meeting, American Society of Gene Therapy, Boston, MA, June 5-9, 2002.
188. G Liu, I Martins, SM Hughes, **BL Davidson**. Transgene positive cells in the ependyma do not migrate to the olfactory bulb. 5th Annual meeting, American Society of Gene Therapy, Boston, MA, June 5-9, 2002.
189. HL Paulson, VM Miller, H Xia, GL Marrs, CM Gouvion, G Lee, **BL Davidson**. Allele-specific silencing of dominant neurodegenerative disease genes. 55th Ann Mtg, American Academy of Neurology, Honolulu, Hawaii, March 29 – April 5, 2003.
190. H Xia, Q Mao, **BL Davidson**. HIV Tat PTD-modified adenovirus: improving gene transfer to CAR negative cells. 6th Annual meeting, American Society of Gene Therapy, Washington DC, June 4-8, 2003.
191. H Xia, Q Mao, N Kiewiet, **BL Davidson.** Characterizing Pol II and Pol III driven siRNA: application to spinal cerebellar ataxia type I. 6th Annual meeting, American Society of Gene Therapy, Washington DC, June 4-8, 2003.
192. SQ Harper, PD Staber, SK Fineberg, HL Paulson, **BL Davidson**. Silencing huntingtin with siRNA. 6th Annual meeting, American Society of Gene Therapy, Washington DC, June 4-8, 2003.
193. SQ Harper, PD Staber, SK Fineberg, HL Paulson, **BL Davidson**. Silencing huntingtin with siRNA. University of Iowa College of Medicine Research Day, April 2, 2003.
194. DA Machado-Aranda, Y Adir, JI Sznajder, DA Dean. Efficient gene transfer of the $Na^{=}/K^{=}$-ATPase ß-2 subunit in rat lungs using electroporation. American Thoracic Society meeting, Seattle, WA, May 16-21, 2003.
195. JL Young, D Machado-Aranda, K Blair-Parks, DA Dean. Gene transfer to the murine lung using electric fields. American Thoracic Society meeting, Seattle, WA, May 16-21, 2003.
196. G Liu, Y Chen, IH Martins, JA Heth, Q Mao, X He, JA Chiorini, **BL Davidson**. Adeno-associated virus type 5 (AAV5) mediated central nervous system functional correction in mucopolysaccharidosis type VII mice. Society for Neuroscience, 33rd Annual meeting, New Orleans, LA, November 8-12, 2003.
197. MC Bohn, **BL Davidson**, K Bankiewicz, X Breakefield. Gene therapy in the CNS: novel vectors for imaging and regulating gene expression. 37th Winter Conference on Brain Research, Copper Mountain, CO, January 24 – 30, 2004.
198. CS Stein, I Martins, **BL Davidson**. The lymphocytic choriomeningitis virus envelope glycoprotein targets lentivirus to neural progenitors in the murine brain. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
199. YH Chen, **BL Davidson**. Targeting AAV to brain vascular endothelium. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
200. R Boudreau, H Xia, **BL Davidson**. Micro RNAs as novel siRNA shuttles. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
201. G Liu, JA Chiorini, **BL Davidson**. AAV4 mediated gene transfer in mucopolysaccharidosis type VII mice. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.

202. H Xia, Q Mao, SL Eliason, N Kiewiet, J Critchfield, IH Martins, SQ Harper, X He, RM Kotin, HY Zoghbi, HT Orr, HL Paulson, **BL Davidson**. RNAi therapy for dominant neurodegenerative diseases. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
203. G Liu, RM Kotin, JA Chiorini, **BL Davidson**. Neuroal progenitor cell transduction with AAV serotypes 1 and 4. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
204. SQ Harper, PD Staber, CR Rowley, X He, IH Martins, Q Mao, HL Paulson, **BL Davidson**. Gene silencing of human huntingtin using lentivirus-delivered shRNA. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
205. Y Kang, TE Scheetz, CJ Moressi, DT Tran, L Xie, **BL Davidson**, TL Casavant, PB McCray Jr. *In vitro* and *in vivo* analysis of feline immunodeficiency virus-based lentiviral vector integration. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
206. Y Kang, L Xie, DT Tran M Hickey, C Stein, **BL Davidson**, PB McCray Jr. Enhancing hepatocyte gene transfer with baculovirus GP64 glycoprotein. 6th Annual Meeting, American Society of Gene Therapy, Minneapolis, MN, June 2-6, 2004.
207. PD Staber, SQ Harper, SL Eliason, CR Rowley, X He, IH Martins, Q Mao, HL Paulson, P Gonzalez-Alegre, **BL Davidson**. Huntingtin gene silencing by lentivirus-delivered shRNA leads to phenotypic improvement in an HD mouse model. Society for Neuroscience 34th Annual meeting, San Diego, CA, October 23-27, 2004.
208. SQ Harper, PD Staber, SL Eliason, X He, IH Martins, Q Mao, HL Paulson, RM Kotin, **BL Davidson**. AAV-delivered RNAi causes cellular and motor improvements in a mouse model for HD. Society for Neuroscience 34th Annual meeting, San Diego, CA, October 23-27, 2004.
209. RL Boudreau, H Xia, SQ Harper, WT Talman, **BL Davidson**. Incubible RNAi-therapy for polyglutamine disease. Society for Neuroscience 34th Annual meeting, San Diego, CA, October 23-27, 2004.
210. GM Borchert, RA Cornell, DC Slusarski, S Ding, **BL Davidson**. miR23 in the developing Zebrafish. Society for Neuroscience 34th Annual meeting, San Diego, CA, October 23-27, 2004.
211. MA Passini, D Sondhi, J Bu, EL Giannaris, E Vassallo, NR Hackett, SM Kaminsky, M El-Banna, Q Mao, M Chang, **BL Davidson**, DE Sleat, P Lobel, RG Crystal, GR Stewart. Intracranial gene delivery of human CLN2 reduces brain pathology in a mouse model of late infantile neuronal ceroid lipofuscinoses (LINCL). Society for Neuroscience 34th Annual meeting, San Diego, CA, October 23-27, 2004.

Reviews

1. Beer SJ, Hilfinger JM, **Davidson BL**. "Extended release of adenovirus from polymer microspheres: Potential use in gene therapy for brain tumors. Advance Drug Delivery Review; 27(1):59-66, 1997.
2. **Davidson BL**. (ed) "Novel Gene Delivery Systems", Advanced Drug Delivery Review, 1997.
3. Rios CD, Chu Y, **Davidson BL**, Heistad DD. Ten Steps to Gene Therapy for Cardiovascular Diseases. J Lab Clin Med 132(2):104-111, 1998.

B. Areas of Research Interest

My laboratory is focused on inherited genetic diseases that cause central nervous system dysfunction, with a focus on the lysosomal storage diseases; the mucopolysaccharidoses and Batten's disease. The aims are to better understand the biochemistry and cellular trafficking of proteins deficient in these disorders, and to develop gene and cell-based medicines for therapy. For gene therapy studies, the focus is on vector development with an emphasis on the examination of novel envelopes for cellular targeting of lentivirus vectors, or novel capsid proteins for encapsidated vectors (AAV and adenovirus). In recent work we demonstrated that the application of these vectors to animal models of storage disease could reverse CNS deficits. Molecular correlates, examined using gene chip arrays, corroborated the beneficial effects of gene therapy.

C. Published reviews of scholarship

D. Grants

Active Support – Not listed

E. Invited Lectures

1992 "CNS-directed Gene Therapy with Recombinant Adenoviruses", Frank K. Kelemen Memorial Symposium, Coriell Institute for Mental Health Research, Camden, NJ
1992 "Gene Therapy to the Central Nervous System", Molecular Medicine at Michigan, University of Michigan Medical School, Ann Arbor, MI
1993 Biochemistry and Neurobiology Sections, Warner-Lambert/Parke-Davis, Ann Arbor, MI
1993 Visiting Professorship, Nebraska Wesleyan Univrsity, Lincoln, NE
1993 Wayne State University, Department of Molecular Biology and Genetics, Detroit, MI, May 17, 1993
1993 Plenary Speaker, "Gene Transfer to Cellular Components of the CNS". First Annual Symposium of the Institute for Human Gene Therapy, University of Pennsylvania, Philadelphia, PA, September 24-25, 1993
1993 "Potentials for Anti-Inflammatory Therapy Using Gene Transfer Techniques", Henry Ford Hospital, October 19, 1993
1994 Invited Panelist, "Viral Vectors for Gene Transfer into the Nervous System: Tools for studying Neuronal Physiology", 27th Winter Conference on Brain Research, Snowbird, UT, January 22-29, 1994
1994 "Adenoviral-mediated Gene Transfer into the CNS: Potential Therapeutic Applicatons", Harvard Medical School, Massachusetts Eye and Ear Infirmary, Department of Opthalmology, Boston, MA, May 13, 1994
1994 "Development of New Vectors for Gene Therapy", Symposium on Molecular Genetics and Gene Therapy: Applications to Muscle and Synovium, University of Michigan Medical School, Ann Arbor, MI, May 27, 1994
1994 Invited Participant, Workshop on "Approaches for the Treatment of Pulmonary Fibrosis", National Institutes of Health, National Heart, Lung and Blood Institute, Bethesda, MD, August 30-31, 1994
1995 Invited Speaker: Gordon Conference, Oxnard, CA
1995 Invited Speaker: Controlled Release of Bioactive Materials, Seattle, WA
1995 Invited Speaker: Conference on Gene Transfer for CNS Disorders, Philadelphia, PA
1995 "Recombinant Adenoviruses: Potential Therapeutic Application to CNS Diseases:, Schering-Plough Research Institute, Kenilworth, NJ, January 20, 1995
1995 University of Minnesota, "Adenoviral Mediated Gene Transfer to the CNS: Potential Therapeutic Applications", Department of Pharmacology, Minneapolis, MN, April 21, 1995
1995 University of Rochester Medical Center, Anatomy's Spring Seminar Series, Rochester,NY, May 5, 1995
1995 University of Wisconsin, Center for Neuroscience, Madison, WI, May 15, 1995
1996 Cephalon Inc., West Chester, PA, April 19, 1996
1996 Genetic Therapy Inc. "Neurogenic Program Advisory Mtg, Gaithersburg, MD, June 3, 1996
1996 23rd International Symposium on Controlled Release of Bioactive Materials, Kyoto, Japan. "Alternative Formulation of Viral Vectors, July 10, 1996
1996 University of Alabama, Birmingham, AL. "Proliferation induced by growth factors enhances in vivo retroviral-mediated gene transfer to hepatocytes", October 1999
1996 Society for Neuroscience, 26th Annual meeting. "Viral vectors for the study and treatment of inherited disorders of the CNS". November 16-21, 1996
1996 Chiron-Viagene, San Diego, CA, December 1996
1997 Cardiovascular Research Center, University of Iowa, Iowa City, IA "Overcoming barriers to liver directed gene transfer", March 1997
1997 Prostate Cancer Research Conference, University of Iowa, Iowa City, IA
1997 Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO, June 23, 1997

1997 Batten Disease Support and Research Association Conference, San Antonio, TX, July 25, 1997
1997 Institute for Human Gene Therapy 1997 Retreat, Absecon, NJ "Retroviral Gene Transfer to Liver – Revisited", September 21, 1997
1997 American Heart Gene Therapy Symposium, November 1997
1998 Winter Brain Research Conference, Snowbird, UT, January 1998
1998 Invited Speaker, Rotary Club of Iowa City, January 15, 1998
1998 University of Iowa Research Day "Correction of Metabolic Disorders in the CNS with Viral Vectors", February 6, 1998
1998 First Annual Meeting, American Society of Gene Therapy, Seattle, WA, May 1998
1998 The Seventh Annual International Congress on Neuronal Ceroid – Lipofuscinoses (NCL-98), June 1998
1998 Invited Speaker, Genethon, Evry, France, September 1998
1998 Invited Speaker, Pasteur Institute, Paris, France, September 1998
1998 Invited Speaker, International Conference on Gene Therapy, Sweden, September 1998
1998 Invited Speaker, University of Oulu, Oulu, Finland, September 1998
1998 Invited Speaker, Genzyme Corporation, Framingham, MA, October 1998
1999 Invited Speaker, University of Michigan, Ann Arbor, MI March 1999
1999 Invited Speaker, BASF, May 1999
1999 Invited Speaker, Gordon Conference on Neurovirology, New Hampshire, MA, June 1999 (Declined)
1999 Speaker, 2nd Annual Conference, American Society of Gene Therapy, Washington DC, June 1999
1999 Invited Speaker, 5th International meeting of the COGENT Society, Minneapolis, MN, June 1999
1999 Promega Lecturer, Society of Neuroscience, Miami Beach, FL, November 1999
1999 Invited Speaker, Massachusetts General Hospital, December, 1999
2000 Invited Panelist, Winter Conference on Brain Research, Breckenbridge, CO, January 2000
2000 Invited Speaker, Wadsworth Center/David Axelrod Institute, Albany, NY, March 2000
2000 Invited Speaker, University of Toronto, Toronto, Canada, March 2000
2000 Symposia Organizer, FASEB 2000, San Diego, CA April 2000.
2000 Invited Speaker, Chiron Technologies, Center for Gene Therapy, San Diego, CA, April 2000
2000 Invited Speaker, Canji, San Diego, CA, April 2000
2000 Invited Lecturer, University of Puerto Rico at Mayaguez, Puerto Rico, April 2000
2000 Invited Speaker, NCLRA symposium, Washington DC, May, 2000
2000 Invited Speaker, 6th International symposium on Mucopolysaccharidosis and related diseases and International symposium on Innovative Therapies. Minneapolis, MN, May 2000
2000 Session Moderator, American Society of Gene Therapy, Denver, CO, May-June 2000
2000 Invited Speaker, University of Manchester, Manchester, England, September 19, 2000
2000 Invited Speaker, The Eighth International Congress on Neuronal-Ceroid Lipofuscinoses Exeter College, Oxford, England, September 2000
2000 Invited Speaker, Medical and Molecular Genetics Center, L'Hospitalet de Llobregat, Barcelona, Spain, September 27, 2000
2000 Invited Speaker, 14th Annual North American Cystic Fibrosis Conference, Baltimore, MD, November, 2000.
2000 Invited Speaker, Expert Meeting on Adenovirus Mediated Gene Delivery, Merck Research Laboratories, West Point, PA, December 12, 2000 – Invitation declined.
2001 Invited Speaker, 34th Annual Winter Conference on Brain Research, Steamboat Springs, CO, January 2001
2001 Invited Speaker, Molecular Medicine Program, Mayo Clinic, Rochester, MN, March 21, 2001.
2001 Invited Speaker, Simpson College Women in Science program, Women's History Month, Indianola, IA, March 27, 2001
2001 Invited Speaker, Genes and Gene Delivery for Diseases of Alcoholism" symposium, University of North Carolina, NC, May 7-9, 2001
2001 Invited Speaker, 4th Annual meeting, American Society for Gene Therapy, Seattle, WA, May 30 – June 3, 2001

2001 Invited Speaker, Rett Syndrome Research Foundation, Washington DC, June 11-13, 2001
2001 Invited Speaker, National Mucopolysaccharidosis Society (MPS) meeting on "Strategies for therapy of the MPS and related diseases", University of California, Los Angeles campus, June 21-24, 2001.
2001 Invited Speaker, Avigen Inc, Alemeda, CA, June 29, 2001
2001 Invited Speaker, International Society for Neurochemistry/American Society for Neurochemistry Post-satellite meeting "Gene Transfer in Neurosciences: Towards Gene Therapy of the Nervous System", Buenos Aires, Argentina, South America, August 25-31, 2001.
2001 Invited Speaker, 4th Workshop on Mouse Molecular Neurogenetics, September 12 – 15, Jackson Laboratories, Bar Harbor, ME
2001 Invited Speaker, 3rd Conference on Cellular and Molecular Treatments of Neurological Diseases, Harvard Medical School, September 20 – 23, 2001 – meeting re-scheduled.
2001 Invited Speaker, GVPN conference, Fribourg, Switzerland, October 3-5, 2001
2001 Invited Speaker, AAAS conference on "Becoming Human .. and Beyond", Chicago, IL, November 1-3, 2001
2001 Invited Speaker, Wyeth, Princeton, December 3, 2001
2002 Invited Speaker, 35th Winter Conference on Brain Research, Snowmass, CO, Jan-Feb, 2002.
2002 Invited Speaker, 3rd Conference on Cellular and Molecular Treatments of Neurological Diseases, Cambridge, MA, March 13-15, 2002
2002 Invited Speaker, Institute for Human Gene Therapy, Philadelphia, PA, April 29, 2002.
2002 Invited Speaker, Frontiers in Gene Therapy Lecture Series, Stanford University Medical Center, Stanford, CA, May 9, 2002.
2002 Invited Speaker, 13th Annual Virology Symposium on Design and Application of Viral Gene Vectors: Engineering Pathogens into Prescriptions. University of Pittsburgh, Philadelphia, PA, May 14-15, 2002.
2002 Invited Speaker, 5th Annual Meeting, American Society of Gene Therapy, Boston, MA June 5-9, 2002
2002 Invited Speaker, 7th International Symposium on Mucopolysaccharide and Related Diseases/3rd Scientific Lysosomal Storage Disorders Congress, Paris, France, June 20-23, 2002.
2002 Invited Speaker, Hunters Hope 5th Annual Medical and Scientific Symposium, Java, NY, July 5-9, 2002.
2002 Invited Speaker, ALS Gene Therapy Workshop, New York, NY, October 13, 2002.
2002 Invited Speaker, Society for Neuroscience, Orlando, FL, November 2-7, 2002.
2002 Invited Speaker, Angiogenic Gene Therapy: A novel treatment paradigm for CAD: Ad5FGF4 Global Inaugural Workshop, New York, NY, December 13-15, 2002.
2003 Invited Speaker, "Applications of RNA Interference" conference, San Diego, CA, Feb 10-12, 2003/
2003 Invited Speaker, American Society for Microbiology "Rational Gene Therapy: The Next Five Years", Banff, Canada, Feb 26 – March 2, 2003.
2003 Invited Speaker, "siRNA Prospects for New Therapeutics & Commercial Opportunities for Phara and Biotech, San Diego, CA, March 23-24, 2003.
2003 Invited Speaker, 2nd International Symposium on Molecular Diagnostics & Skin Gene Therapy, Dusseldorf, Germany, March 27-29, 2003.
2003 Invited Speaker, "Frontiers in Gene Therapy" lecture series, Stanford University, Stanford, CA, April 10, 2003.
2003 Invited Speaker, American Society of Gene Therapy, Washington DC, June 4-8, 2003.
2003 Invited Speaker, World Congress on Huntington's Disease, Toronto, Canada, August 16-19, 2003.
2003 Invited Speaker, Program in Biomedical Sciences, University of Michigan, Ann Arbor, MI, October 14, 2003.
2003 Invited Speaker, Wadsworth Center Molecular Genetics Program symposium, Albany, NY, October 20, 2003.
2003 Invited Speaker, The American Society of Human Genetics, Los Angeles, CA, November 7, 2003.
2003 Invited Speaker, NINDS workshop, November 13-14, 2003.
2003 Invited Speaker, Cold Spring Harbor symposium "Rat Genomics and Models", Cold

Spring Harbor, NY, December 11-14, 2003.

2004 Invited Speaker, National Institutes of Health, Laboratory of Biochemical Genetics, NHLBI, January 8, 2004

2004 Invited Speaker, 37th Winter Conference on Brain Research, Copper Mt, CO, Jan 24-30, 2004

2004 Invited Speaker, Association for Research in Otolaryngology, Daytona Beach, FL, Feb 24-28, 2004.

2004 Invited Speaker, American Society of Gene Therapy, Minneapolis, MN June 2-6, 2004.

2004 Invited Speaker, 2nd Annual RNA Interference conference, San Francisco, CA, June 20-22, 2004.

2004 Invited Speaker, Molecular Mechanisms of Human Neurology Diseases, Cold Spring Harbor Laboratory, July 6-12, 2004.

2004 Invited Speaker, Batten Disease Support & Research Association (BDSRA) "Reaching Beyond the Rainbow" conference, Kansas City, KS, Aug 5-8, 2004.

2004 Invited Speaker, Hereditary Disease Foundation's Biennial Symposium on Huntington'd Disease, Aug 12-15, 2004

2004 Invited Speaker, Physiological Society of the United Kingdom Viral Symposium, Bristol, United Kingdom, September 2004.

2004 Invited Speaker, NIH Conference on RNA interference – target validation and potential therapeutic applications for childhood cancers, Washington DC, September 28-29, 2004.

2004 Invited Speaker and Short Course 1 organizer, Society for Neuroscience, San Diego, CA, October 24-27, 2004

2005 Invited Speaker, Molecular, Cellular and Clinical aspects of Neurodegenerative Diseases, Verbier, Switzerland, Jan 30 – Feb 2, 2005.

2005 Invited Speaker, Center for Aging and Developmental Biology Seminar Series, University of Rochester, Rochester, NY, Feb 17-18, 2005.

2005 Invited Speaker, Chicago Neural Repair Club, Northwestern University, Chicago, IL, March 8, 2005

2005 Invited Speaker, Northern Illinois University Research Seminar Series, DeKalb, IL, April 1, 2005

2005 Invited Speaker, Iowa State University Biological Sciences Seminar Series, Ames, IA, April 6, 2005

2005 Invited Speaker, "Gene Therapy State of the Art" Joint Conference – Royal Society of Medicine, International Association for Biologicals (IABs); Center for Biologicals Evaluation and Research (CBER); and US Food and Drug Administration (FDA), London, UK, April 25, 2005.

2005 Invited Speaker, Children's Hospital of Philadelphia Research Group, Cell and Gene Therapy Seminar Series, Philadelphia, PA, May 23, 2005

2005 Invited Lecturer, Monroe J Lustabder Memorial lecturer, Rutgers University, New Brunswick, NJ, May 24, 2005

2005 Invited Speaker, American Society of Gene Therapy 9th Annual Meeting, St. Louis, MO, June 1-5, 2005.

2005 Invited Speaker, 10th International Congress on Neuronal Ceroid Lipofuscinosis (NCL), Helsinki, Finland, June 5-8, 2005.

2005 Invited Speaker, CG triplet repeats, Gordon Conference, Mt Holyoke, MA, July 24-29, 2005

2005 Invited Speaker and Short Course Organizer, Society for Neuroscience, Washington, DC, November 12-16, 2005.

IV. SERVICE

A. Offices held

Editorships

1991-- Ad hoc reviewer, *The Journal of Molecular Biology*

1992-- Ad hoc reviewer, *The Journal of Clinical Investigation, Nature Genetics Nucleic Acids Research, Human Genetics*

1993-- Ad hoc reviewer, *The American Journal of Human Genetics*
1993-- Ad hoc reviewer, *Human Gene Therapy, Gene Therapy, Neuroscience Letters*
1994-- Ad hoc reviewer, *Behavioral and Brain Sciences (BBS), Nature Medicine, Nature Biotechnology, Proceedings of National Academy of Sciences, Journal of Virology, Circulation Research, Hypertension, Biotechniques, Arthritis Thrombosis and Vascular Biology, Stroke, Reviews in Mutation Research, European Journal of Neuroscience*
1998-- Associate Editor, *Journal of Gene Medicine*
1999 Associate Editor, *Arteriosclerosis, Thrombosis, and Vascular Biology*
1999-- Editorial Board, *Gene Therapy*
2000 External Reviewer, *Human Frontier Science Program Organization*
2000 Editorial Board, *Molecular Therapy*
2000 Associate Editor, *Current Gene Therapy*
2003-06 Associate Editor, *Molecular Therapy*
2005-07 Editorial Board, *Human Gene Therapy*

Review Panels

1993 *Ad hoc* reviewer, National Retinitis Pigmentosa Foundation
1993-94 Reviewer, Office of the Vice President for Research, University of Michigan
1993-94 Biological Research Review Committee (Institutional biosafety Committee) Office of the Vice President for Research, University of Michigan
1994 *Ad hoc* reviewer, National Cancer Foundation, United States-Israel Bi-national Foundation
1994-98 NINDS, NICHD, Special Review Committee, MRRC Site Visit Team
1999 *Ad hoc reviewer,* NINDS, Neurology Study Section
1998-01 Ad hoc reviewer, Howard Hughes and Carver Trust fellowships
1999-01 Iowa Biosciences Review Committee
1994 *Ad hoc* reviewer, National Institutes of Health: NINDS, RFA Special Review
1996 Committee, Medical Biochemistry Study Section
1995-99 Member, Mental Retardation Research Committee, National Institute of Child Health and Human Development (NICHD)
1996-- *Ad hoc* reviewer, Cystic Fibrosis Research Center
1997 *Ad hoc* reviewer, University of Iowa, HHMI – Pilot Grants
1999-- Reviewer, NIH Grant Review Committee
1999-- Reviewer, NICHD Grant Review Committee
1999 *Ad Hoc* member, NSDB Review Committee, NINDS, NIH, Seattle, 10/99
2000 *Ad Hoc* reviewer, Gene Therapy and Therapeutics Laboratory, National Institutes of Health (intramural)
2001 *Ad Hoc* member, RSRF Scientific Advisory Board
2002 Reviewer, NIH BDCN Grant Review Committee
2002-- Reviewer, ALS Association

Departmental, collegiate, university and national committees

1994 Member, *Molecular Biology program*, University of Iowa College of Medicine
1995-99 Member, *Mental Retardation Research Committee*, National Institute of Child Health and Human Development (NICHD)
1995-98 Member, *Research Advisory Council*, University of Iowa College of Medicine, Office of the Dean
1995-- Member, The Parkinson's Disease Gene Therapy Consortium
1996-- Member, National Gene Vector Laboratory Scientific Review Board
1996-98 Co-Chair, College of Medicine Research Week, University of Iowa College of Medicine
1996-- Member, Neuroscience Interdisciplinary Graduate Degree Program, University of Iowa
1996-- Member, Interdisciplinary PhD Program in Genetics, University of Iowa College of Medicine
1997-- Member, Scientific Committee – Neuromuscular Disorders, American Society for Gene Therapy

1997-- Member, Admissions Committee, Opportunities for Interdisciplinary Research in Biomolecular Sciences (ORBS)
1997-99 American Heart Association, Midwest Regional Consortium
1997-99 Member, ORBS Graduate Admissions Committee
1998-- Member, Biosafety Level III Facility Advisory Committee
1996-97 Member, University of Iowa College of Medicine Research Retreat Working Group in Training and Recruitment
1998-- Chair, Cancer Center Space Committee, University of Iowa
1998 Virology Training Grant Committee, University of Iowa
1998 Virology Search Committee, University of Iowa
1998 Neurology Departmental Review Committee, University of Iowa
1998 Chair, Admissions Committee, Molecular Biology Training Program, University of Iowa
1999-- Member, Biosciences Graduate Admissions Committee
1999 Member, Biosciences Initiative Steering Committee, University of Iowa
1999-- American Society of Gene Therapy, Organization Committee
2000 Organizer, Symposia entitled "Cells and Genes and their Applications for Therapies for the Brain I" and "Cells and Genes and their Applications for Therapies for the Brain II", FASEB, San Diego, California, April 16, 2000.
2000 Moderator, American Society of Gene Therapy session entitled "Cell Therapy for Muscle and Brain", Denver, Colorado, June 3, 2000
2000-01 Chair, *Transgenic and Gene Targeting Facility Advisory Committee*, University of Iowa College of Medicine
2000-- Senior Member, *Center for Macular Degeneration*, University of Iowa College of Medicine
2000-02 Member, *Executive Committee, Neuroscience Graduate Program*, University of Iowa College of Medicine
2000-03 Member, Board of Directors, *American Society of Gene Therapy*
2000 Member, *Ad hoc Neurosurgery Search Committee*, University of Iowa
1999-03 Consultant, *Hunters Hope Foundation*
1999-- Consultant, *Curtis Foundation*
2000-- Member, *Scientific Advisory Board,* Batten Disease Support & Research Association (BDSRA)
2000-- Consultant, *Selective Genetics*
2001-02 Chair, *American Society of Gene Therapy* Neural Disorders Gene Therapy Committee
2001-04 Member, *Transgenic Facility Advisory Committee*, University of Iowa College of Medicine
2001-03 Member, *Gene Targeting Facility Advisory Committee*, University of Iowa College of Medicine
2001-03 Member, *Research Committee*, University of Iowa College of Medicine
2001-- Member, *Scientific Advisory Board*, Biomedica Inc
2002-03 Chair, *American Society of Gene Therapy*, Neural Disorders Committee
2002-04 Member, *Scientific Review Board,* National Gene Vector Laboratories
2002-04 Chair, *Gene Targeting Facility Advisory Committee*, University of Iowa College of Medicine
2002-04 Member, *Biosafety Level III Facility Advisory Committee,* University of Iowa College of Medicine.
2002-03 *Ex Officio* Member, *Gene Vector Core Committee*, University of Iowa College of Medicine
2002-03 Member, *Research Committee*, University of Iowa College of Medicine
2002-03 Member, *Transgenic Facility Advisory Committee*, University of Iowa College of Medicine
2003-- Member, *Presidential Biological Scholar Program Steering Committee*, University of Iowa College of Medicine
2003-- Member, *Scientific Advisory Board*, Sirna Therapeutics
2004-- Member, *Cardiovascular Research Center Executive Committee*, University of Iowa
2004-05 Member, *Graduate Student Affairs Committee*, University of Iowa
2005-08 Treasurer, American Society of Gene Therapy

Other

Professional Affiliations

Year	Affiliation
1999--	American Association for the Advancement of Science
1994-98	American Federation for Clinical Research – Midwest Section
1996--	American Society for Neuroscience
1997--	American Society of Gene Therapy
1998--	American Society for Microbiology

Patents

US Patent 5,647,072	"Adenoviral-Mediated Gene Transfer to Synovial Cells *In Vivo*" Davidson and Roessler
US Patent 6,468,524 B1	"AAV5 Vector and Uses Thereof" Chiorini, Zabner and Davidson
US Patent 6,830,920 B2	"Rapid Generation of Recombinant Adenoviral Vectors" Davidson, Anderson, Haskell, Xia
US Patent 6,262,035 B1	"Gene Replacement Therapy for Mucular Dystrophy" Campbell, Davidson, Williamson, Lim, Duclos, Straub, Holt
US Patent 6,635,466B2	"Adenovirus serotype 30 (AD30)" Davidson and Law
US Patent 6,855,549	"Methods and compositions for increasing the infectivity of gene transfer vectors" McCray, Wang, Davidson, Bodner, Herrmann, Jolly.

Patents Pending

DHHS: E-071-00/0	"AAV4 Vector and Uses Thereof" Chiorini, Kotin, Safer, Davidson
USSN 08/824.997	"Microsphere Encapsulation of Gene Transfer Vectors" Davidson and Hilfinger
DHHS: E-072-00/0	"AAV5 Vector for Transducing Brain Cells and Lung Cells" Chiorini, Kotin, Safer, Davidson, Zabner

"Methods of Tranducing Cerebellar Neurons Using Lentivirus Vectors" Davidson, Sauter, Dubensky

"Use of Recombinant Gene Delivery Vectors for Treating or Preventing Lysosomal Storage Disorders" Davidson, Sauter, Dubensky

Inventions

"PTD.Ad" Davidson, Xia

"RAPAd" Davidson, Anderson, Haskell, Xia

Trademark

"RAPAd" Davidson, Anderson, Haskell, Xia

B. **Clinical Assignments** : Not applicable

Commentary

Brain-directed gene therapy for lysosomal storage disease: Going well beyond the blood–brain barrier

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The lysosomal storage diseases (LSDs) are a heterogeneous group of disorders that affect 1/7,000 live-born infants, the majority of which develop central nervous system (CNS) disease. Brooks *et al.* (1) report exciting results from Davidson's group with brain-directed gene therapy for murine mucopolysaccharidosis (MPS) VII that are likely to have general implications for the treatment of CNS disease in LSD. Each LSD results from a deficiency of a single lysosomal enzyme important for degrading macromolecules that must be turned over in lysosomes. More than 40 LSDs have been described (2). Over the past two decades, dramatic progress has been made in understanding the biogenesis, structure, and function of lysosomes and the processes by which newly synthesized acid hydrolases are assembled, processed, and transported to lysosomes.

Understanding the receptors that target enzymes to lysosomes led to the development of successful enzyme replacement therapy.

Understanding the receptors that target enzymes to lysosomes, some of which are expressed on the cell surface, led to the development of successful enzyme replacement therapy for one of the LSDs, Gaucher Disease, a disorder of sphingolipid degradation (3). Gaucher Disease results from deficiency of glucocerebrosidase (β-glucosidase), the enzyme involved in the last step of sphingolipid degradation. Storage of glucocerebroside in macrophages produces tremendous enlargement of spleen and liver, disabling bone involvement and occasional pulmonary incapacity. The strategy for treatment involved purification of placental enzyme and later recombinant enzyme from Chinese hamster ovary cell secretions and modification of the native enzyme to expose mannose residues on oligosaccharides. This strategy targets the infused enzyme to the mannose receptors of fixed-tissue macrophages, precisely the cells affected by the storage; receptor-mediated endocytosis delivers enzyme to the lysosomes where the substrate is stored. Over 3,500 Gaucher Disease patients have been treated since the early 1990s, and the treatment is considered a clinical success (4). The major form of Gaucher Disease does not have CNS involvement. However, the less common neuropathic forms of Gaucher Disease will require a strategy for the enzyme to reach the CNS.

Another apparent success in the treatment of LSD is enzyme therapy for Fabry Disease, another sphingolipid disorder that does not produce lysosomal storage in the CNS (5). This LSD affects primarily vascular endothelial cells and results from a deficiency of α-galactosidase A, which leads to the pathological accumulation of globotriaosylceramide (GL3) and related glycosphingolipids in these cells. Kidney involvement leads to loss of renal function in the third or fourth decade of life. This disease does not affect brain directly, so enzyme access to brain is not required, but it does eventually lead to cerebral vascular insufficiency because of endothelial damage. Two clinical trials of enzyme produced by two different companies were reported recently (6, 7). Although both appear very promising, long-term data are not yet available. Both products have been approved for clinical use in Europe, and approval for both has been sought in the United States.

The MPS storage disorders are also moving up to the plate for enzyme replacement with clinical trials for MPS I (Hurler Disease, α-L-iduronidase deficiency) already reported (8), trials for MPS II (Hunter Disease, α-L-iduronidate sulfate deficiency) under way, and trials for MPS VI (Maroteaux–Lamy Disease, *N*-acetylgalactosamine-4-sulfatase deficiency) are just beginning. Although MPS VII (Sly Disease, β-glucuronidase deficiency) may be among the last of these disorders to be treated, it played an important role in the evolution of enzyme replacement therapy for the whole group of LSDs (9). Because it appears unlikely that infused lysosomal enzymes will cross the blood–brain barrier, there is not much optimism that i.v. administered enzyme alone will correct the CNS storage present in most of the MPS disorders.

Like the MPS, most of the other LSDs also have CNS involvement and therefore require a strategy for getting enzyme beyond the blood–brain barrier to achieve correction. A number of groups using a variety of viral vectors and enzyme-producing cells have achieved expression of enzyme in brain of animal models (10–17). Impressive degrees of clearing of local, and in some cases distant, storage have been demonstrated. These experiments raised hopes that arresting progression of CNS pathology was possible through brain-directed gene therapy. What few dared to hope was that this approach would not only prevent progression but also erase neurologic deficits. That is just what Davidson's group reports (1).

The authors (1) show that established CNS storage and the related functional deficits in MPS VII mice can be ameliorated by viral-mediated gene therapy. The lentivirus feline immunodeficiency viral vector they used transduced terminally differentiated cells in the brain and mediated β-glucuronidase (GUSB) gene transfer into CNS cells in adult MPS VII mice. This treatment resulted in secretion of GUSB from transduced cells and uptake by nontransduced cells, leading to reduction in preexisting established brain LSD. Correlating with the reduction in storage in the CNS, these adult mice with

See companion article on page 6216.

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established behavioral abnormalities related to the lysosomal storage had dramatic improvement in spatial learning and memory when GUSB was expressed. Finally, the correction of the pathology and cognitive improvement were accompanied by changes in expression of genes that have been associated with neuronal plasticity. These observations are particularly important because, as the authors point out, most patients with LSD are not diagnosed until they have established lysosomal storage lesions and functional defects. Recovery of function rather than protection from disease onset is a key goal for any effective therapy for human LSD, because most patients are diagnosed well after onset of CNS disease.

The model the authors (1) chose to study is murine MPS VII, the mouse model for human MPS VII or Sly Disease, which results from GUSB deficiency (18). MPS VII is one of the rarest of the human mucopolysaccharide storage disorders, each of which is produced by deficiency in one of the enzymes involved in the degradation of glycosaminoglycans (GAGs), formerly called mucopolysaccharides. Its importance in the evolution of our understanding of lysosomal enzyme targeting outweighs its clinical significance. When first discovered in the early 1970s, MPS VII had one unique feature among the MPS disorders: the deficient enzyme, GUSB, had been purified and characterized several years before the disease was identified. Addition of GUSB was shown to prevent and correct the accumulation of GAGs in fibroblasts from MPS VII patients (19, 20). Thus, MPS VII immediately attracted attention as a model to study enzyme replacement therapy. Studies of the cultured skin fibroblast model system led to the discovery that uptake of GUSB depends on cell surface receptors that recognize phosphate-containing sugar moieties (Man6-P) on the enzyme (21). The Man6-P residues are added to the GUSB and other acid hydrolases as a means of targeting intracellular enzymes

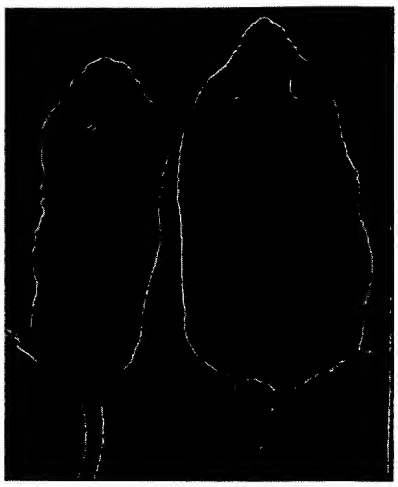

Fig. 1. An adult MPS VII (Sly Disease) mouse (*Left*) is much smaller than its phenotypically normal littermate (*Right*) and has facial dysmorphism with a broad shortened nose and short limbs.

to lysosomes. Another receptor was identified when injected GUSB, from which phosphate had been removed, was found to be rapidly taken up by fixed-tissue macrophage receptors that recognize exposed mannose residues (22). These studies paved the way for Brady and associates to develop "mannose-targeted" cerebrosidase for the treatment of Gaucher Disease (3, 4). These early findings naturally heightened hopes that enzyme replacement in MPS VII patients might lead to correction of lysosomal storage lesions in this disorder. However, MPS VII proved to be too rare (fewer than 100 cases recognized) and too variable to allow controlled experiments to evaluate the response to enzyme therapy.

Nonetheless, hopes for therapy for this and related disorders were greatly advanced by the discovery by Birkenmeier *et al.* at The Jackson Laboratory that GUSB deficiency in mice produces a disorder resembling Sly Disease in humans (23). (Fig. 1) MPS VII mice have a degenerative disease with progressive disability that reduces life span from an average of 28 to just 5 months. Progressive accumulation of undegraded glycosaminoglycans in lysosomes affects the spleen, liver, kidney, cornea, brain, heart valves, and skeletal system and produces widespread organ dysfunction. Progressive hearing loss leads to early deafness, and defects in learning and memory are evident (24–26).

The MPS VII mouse, with a well characterized and uniform genetic constitution and a relatively short life span, proved an attractive model to study experimental therapies for LSD. Mice with MPS VII responded well to bone marrow transplantation, although there was little reduction in brain storage vesicles (27, 28). Enzyme replacement using recombinant GUSB elicited dramatic improvements in visceral pathology but little change in the lyosomal storage lesions in brain unless given to newborns (29–32). Infused GUSB did not cross the blood–brain barrier in mice after 2 wk of age (32). Many promising studies have been reported recently by using this model to study gene therapy, including therapy for CNS storage (10–17). Brain-directed gene therapy, in which viral vectors were introduced directly into the brain, proved one way to bypass the blood–brain barrier, and several studies showed evidence of clearance of CNS storage. However, until now, none of these studies addressed the question raised by Brooks *et al.* (1): whether therapy that corrected the typical cellular pathology in brain could also erase preexisting neurological deficits. For this reason, the study by Davidson's group represents a major advance in this area.

Given the rapidly expanding number of animal models of LSD with CNS involvement and the generality of the biology of lysosomal enzyme transport, these studies are likely to be replicated in other animal models. If the results in other animal models turn out to be as promising as those presented for murine MPS VII, this study will likely be viewed as a landmark that took us well beyond the blood–brain barrier.

COMMENTARY

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RESEARCH ARTICLE

Viral-mediated delivery of the late-infantile neuronal ceroid lipofuscinosis gene, TPP-I to the mouse central nervous system

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Classical late-infantile neuronal ceroid lipofuscinosis (LINCL) is caused by mutations in tripeptidyl peptidase I (TPP-I), a pepstatin-insensitive lysosomal protease, resulting in neurodegeneration, acute seizures, visual and motor dysfunction. In vitro studies suggest that TPP-I is secreted from cells and subsequently taken up by neighboring cells, similar to other lysosomal enzymes. As such, TPP-I is an attractive candidate for enzyme replacement or gene therapy. In the present studies, we examined the feasibility of gene transfer into mouse brain using recombinant adenovirus (Ad), feline immunodeficiency virus (FIV) and adeno-associated virus (AAV) vectors expressing TPP-I, after single injections into the striatum or cerebellum. A dual TPP-I- and β-galactosidase-expressing adenovirus vector (AdTTP-I/nlsβgal) was used to distinguish transduced (β-galactosidase positive) cells from cells that endocytosed secreted TTP-I. Ten days after striatal injection of AdTTP-I/nlsβgal, β-galactosidase-positive cells were concentrated around the injection site, corpus callosum, ependyma and choroid plexus. In cerebellar injections, β-galactosidase expression was confined to the region of injection and in isolated neurons of the brainstem. Immunohistochemistry for TPP-I expression showed that TPP-I extended beyond areas of β-galactosidase activity. Immunohistochemistry for TTP-I after FIVTTP-I and AAV5TTP-I injections demonstrated TPP-I in neurons of the striatum, hippocampus and Purkinje cells. For all three vectors, TPP-I activity in brain homogenates was 3–7-fold higher than endogenous levels in the injected hemispheres. Our results indicate the feasibility of vector-mediated gene transfer of TPP-I to the CNS as a potential therapy for LINCL.
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Introduction

The neuronal ceroid lipofuscinoses (NCLs) are a group of diseases related by accumulation of storage pigments in secondary lysosomes. Historically patients were classified by the ultrastructural morphology of the storage deposits and clinical course.[1,2] One type of NCL is the classical late-infantile form, late-infantile neuronal ceroid lipofuscinosis (LINCL), also known as Jansky–Bielschowsky disease and CLN2 deficiency and pepinase deficiency.[3] LINCL is an acute seizure disorder that begins between 4 and 6 years of age, with rapid deterioration in visual, motor and cognitive functioning. Lysosomal accumulations are evident by electron microscopy as curvilinear osmophilic deposits in tissue biopsies. The deposits consist predominantly of ATP synthase subunit c,[4] a hydrophobic 75 amino acid lipoprotein normally localized in the inner mitochondrial membrane. Recently, gene mapping and functional genomics has allowed identification of the disease allele, and classification of patients based on specific genetic lesions.[5]

Classical LINCL is caused by deficiency of the 46-kDa amino-tripeptidyl peptidase (TPP-I), a lysosomal serine protease with activity on peptides of less than 15 kDa.[5–8] TPP-I, which traffics via the classical mannose-6-phosphate receptor mechanism, is synthesized as a glycosylated 66 kDa inactive precursor that is auto-activated at acidic pH to remove a 20 kDa propeptide.[9] The relationship between subunit c accumulation and TPP-I deficiency is unclear, however data support a requirement for TPP-I early in the progressive enzymatic degradation of ATP synthase subunit c.[10,11]

Current therapy for LINCL can only ameliorate the seizure disorder through conventional anti-epileptic drugs, but cannot change the natural history of the disorder. This would require correcting the underlying cause of lysosomal accumulation by delivery of TPP-I, or genes expressing it, to the brain. Like the soluble lysosomal enzymes arylsulfaltase A and β-glucuronidase, TPP-I is secreted from expressing cells *in vitro*, and endocytosed into non-expressing cells.[12–14] β-Glucuronidase and arylsulfaltase A are also capable of being transported in a retrograde fashion from the site of secretion. Earlier studies in animal models of the lysosomal storage diseases metachromatic

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leukodystrophy and β-glucuronidase deficiency support the ability of directed gene expression for broadly distributed enzyme activity and correction of storage deficits.[14–19] We hypothesize that, similarly, focal TPP-I expression in brain may result in enzyme activity beyond the zone of transduced cells.

Currently, the lack of an animal model precludes testing enzyme and/or gene therapy strategies for the CNS deficits of LINCL. However, viral vectors that direct high-level expression of TPP-I allow us to make an initial assessment of enzyme spread following CNS gene transfer with recombinant adenovirus (Ad), feline immunodeficiency virus (FIV) and adeno-associated virus type 5 (AAV5) vectors. FIV results in focal transduction when delivered to brain.[19,20] Ad leads to local transduction but also moves along white matter tracts, such as the corpus callosum, for transduction of ependyma lining the ventricles.[15,16] AAV5-derived vectors infect a relatively large volume within the mouse brain.[20,21] In the current study, TPP-I wild-type mice (C57BL/6) were injected with Ad, FIV or AAV5 vectors encoding TPP-I into the striatum or cerebellum, and the levels and distribution of TPP-I assessed using immunohistochemistry and enzymatic assays.

Results

We first determined the nature of TPP-I secreted from virally transduced cells *in vitro*. A549 cells were infected with AdTPP-I, FIVTTP-I or AdnlsβgaI (control) and TPP-I activity in the media measured 48 h later. There was no measurable activity in supernatants, indicating that either TPP-I was not secreted or was secreted in the inactive form. As stated earlier, the unprocessed enzyme is inactive, with activation requiring removal of the 20 kDa pro-peptide by auto-activation at pH<4.5. Incubation of harvested supernatants in citrate buffer pH 4.2 for 30 min prior to the addition of the substrate resulted in significant increases in TPP-I activity, up to 1000 times that of the control medium. Thus, secreted TPP-I was predominantly in the inactive form (Figure 1a). In contrast, TPP-I in cell lysates was active. The 100-fold difference in cell-associated TTP-1 activity between FIV- and Ad-infected cells did not correlate to greater enzyme activity in the conditioned media of AdTTP-infected cells, suggesting that the limits of TTP-1 secretion are reached when activity approaches ~seven-fold over endogenous levels.

To determine if LINCL fibroblasts could activate exogenously derived TPP-I, a conditioned medium was

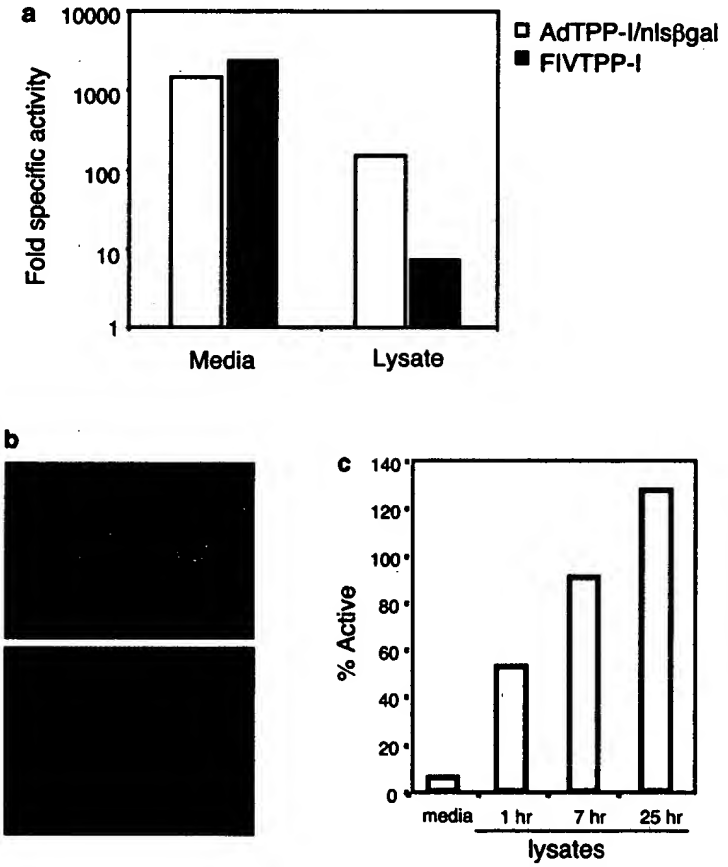

Figure 1 TPP-I activation and uptake in vitro. (a) TPP-I activity levels in cell lysates and media following infection of A549 cells with AdTPP-I/nlsβgal or FIVTPP-I, or mock infected. Enzyme activity was normalized to mock-infected A549 cells. TTP-I in media samples was autoactivated by incubation in citrate buffer pH 4.0 for 30 min. (b) LINCL cells containing a splice junction and non-sense mutation (RMO5387), immunostained 48 h after culture in TPP-I-enriched media. Cells demonstrated TPP-I immunoreactivity (top panel), in contrast to cells cultured in control media (bottom panel). (c) TPP-I activity in LINCL fibroblast cell lysates following incubation in conditioned media from AdTPP-I/nlsβgal-infected A549 cells.

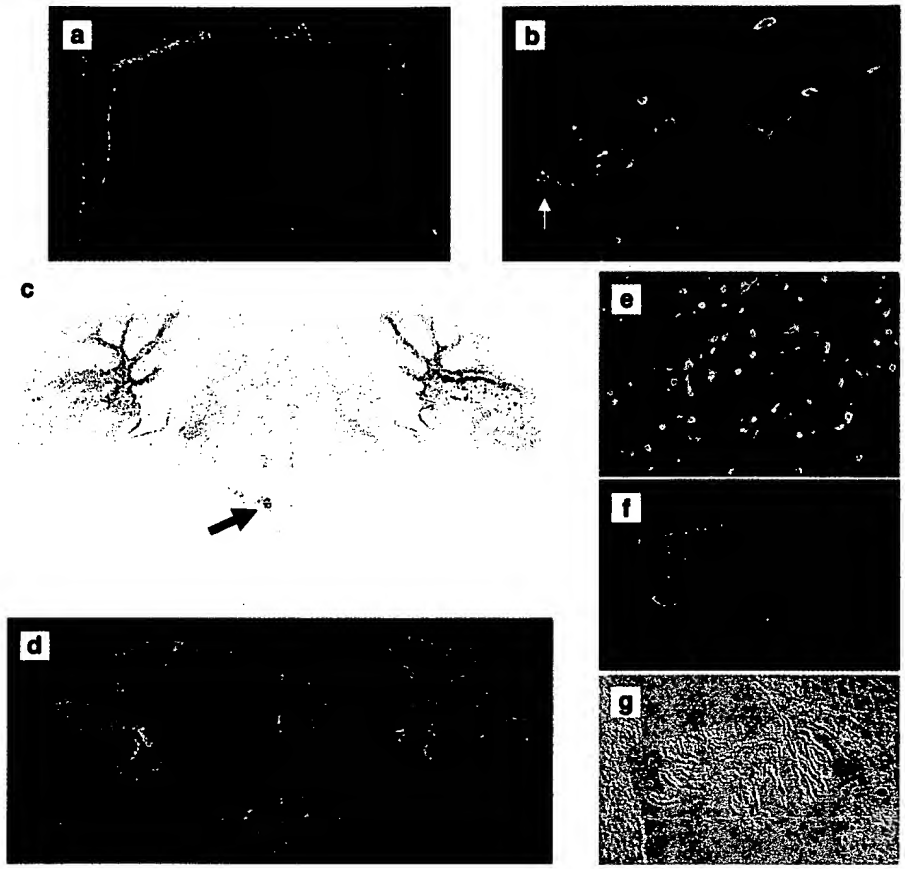

Figure 2 AdTPP-I/nlsβgal expression in the cerebrum and cerebellum 10 days post-injection. (a) Photomicrograph depicting TPP-I (green) and nlsβgal (red) immunoreactivity. (b) TPP-I-positive cells in the absence of β-galactosidase immunoreactivity (arrow) demonstrating uptake of TPP-I in the injected hemisphere. (c) β-Galactosidase expression in the cerebellum after injection of AdTTP-I/nlsβgal into the cerebellar cortex. Note the high concentration of positive nuclei primarily in the white matter tracts of the arbor vitae and also neurons in the brain stem (arrow). (d) TPP-I immunoreactivity in the section adjacent to c. (e) Dual IHC for TTP-I (green) and NeuN (red), in the brainstem. This area from c, arrow. (f) TTP-I-positive cells in the choroid plexus from d. (g) Section adjacent to F stained for β-galactosidase expression.

prepared by infecting A549 cells with AdTPP-I/nlsβgal or the control virus, Adnlsβgal. AdTPP-I/nlsβgal expressed TPP-I and nuclear-localized β-galactosidase (nlsβgal) in the E1 and E3 regions of the adenovirus genome, respectively. TPP-I and nlsβgal were expressed from the CMV or RSV promoter. LINCL fibroblasts were cultured for 48 h with conditioned or control medium from AdTPP-I/nlsβgal- or Adnlsβgal-infected A549 cells, respectively, and then stained for TPP-I immunoreactivity. TPP-I was localized to structures consistent with lysosomal/endosomal compartmentalization (Figure 1b). There was no immunoreactivity in cells treated with Adnlsβgal-conditioned supernatant. The supernatant and cell lysates were assayed 1, 7 or 25 h after addition of media (Figure 1c). Less than 10% of the TPP-I was active in the conditioned media. After 1 h, 50% of the cell-associated TPP-I was active. By 7 and 25 h, 90% and 100% of the endocytosed TPP-I was converted to active enzyme, respectively. These data demonstrate that TPP-I-deficient cells effectively endocytosed and trafficked TPP-I to acidic compartments for activation.

The secretion of TPP-I from transduced cells after injection of 7×10^9 infectious units (i.u.) of AdTTP-I into mouse brain was evaluated. The nuclear-targeted β-galactosidase allowed for identification of transduced cells (nlsβgal$^+$/TPP-I$^+$) *versus* those that had taken up TPP-I only (TPP-I$^+$/βgal$^-$). As shown in Figure 2a, IHC demonstrated TPP-I immunoreactivity in the corpus callosum, the ependyma, and the striatum following striatal injection. The majority of TPP-I-positive cells also contained β-galactosidase-positive nuclei, however some cells were clearly TPP-I$^+$/βgal$^-$ (Figure 2b, arrow) indicating that secretion and uptake had occurred. In cerebella injected with AdTPP-I/nlsβgal (2.9×10^9), β-galactosidase (Figure 2c) and TPP-I immunoreactivity (Figure 2d) were highest in the white matter tracts near the injection site. Radial projections and cell bodies of Bergman glia were also strongly positive for TPP-I immunoreactivity and β-galactosidase (not shown). Isolated βgal$^+$ cells in the brainstem (Figure 2c, arrow) were both NeuN and TPP-I positive (Figure 2e). TPP-I immunoreactivity in these cells resulted from retrograde transport of AdTPP-I/nlsβgal, rather than uptake and subsequent transport of TPP-I. TPP-I$^+$/βgal$^-$ cells were particularly notable in the choroid plexus of the 4th ventricle, indicating that these non-transduced ependymal

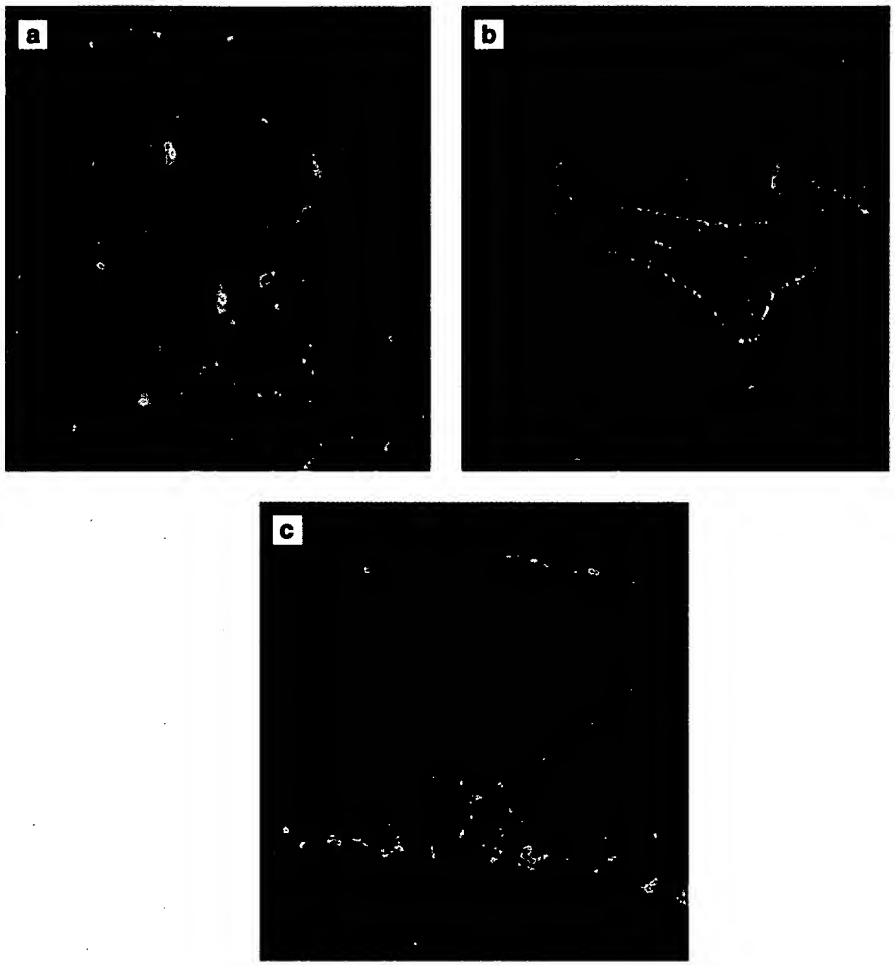

Figure 3 FIVTPP-I-mediated gene transfer to the cerebrum (a) and cerebellum (b,c). (a) TPP-I-positive, NeuN-positive cells in the striatum. (b) TPP-I immunoreactivity in Purkinje cells. (c) TPP-I staining of Purkinje cell bodies and dendrites extending into the molecular layer.

cells had endocytosed TPP-I secreted into the CSF (Figures 2f and g). Immunohistochemical analyses on naïve control brain sections were consistently negative using this rabbit polyclonal antisera (Methods).

We next tested expression from FIV- and AAV-based vectors in murine brain. In striata injected with 2.5 x 10^6 FIVTPP-I, TPP-I immunoreactivity was limited to the injection site and below the corpus callosum. Dual staining 10 days after injection demonstrated that the majority of TPP-I-positive cells were also positive for the neuronal marker NeuN (Figure 3a). Similar results were obtained at 16 and 33 weeks post-injection (not shown). Injections of FIVTPP-I (1 x 10^6 i.u) into the cerebellum resulted in TPP-I immunoreactivity in Purkinje cells and their dendrites (Figures 3b and c). For AAV5TPP-I (5 x 10^9 pt), we examined the distribution of TPP-I 10 weeks after striatal administration. TPP-I immunoreactivity was detected in sagittal brain slices several millimeters caudal to the injection site, especially in the hippocampus (Figure 4). This is consistent with earlier results showing that AAV5 transduces hippocampal neurons

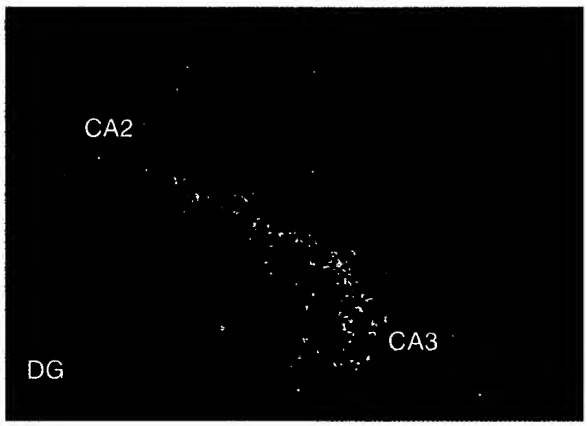

Figure 4 Expression of TPP-I 10 weeks after AAV5TPP-I injection into the cerebrum. A representative sagittal section is shown. TPP-I immunoreactivity was evident in CA2 and CA3 of the hippocampus. DG, dentate gyrus.

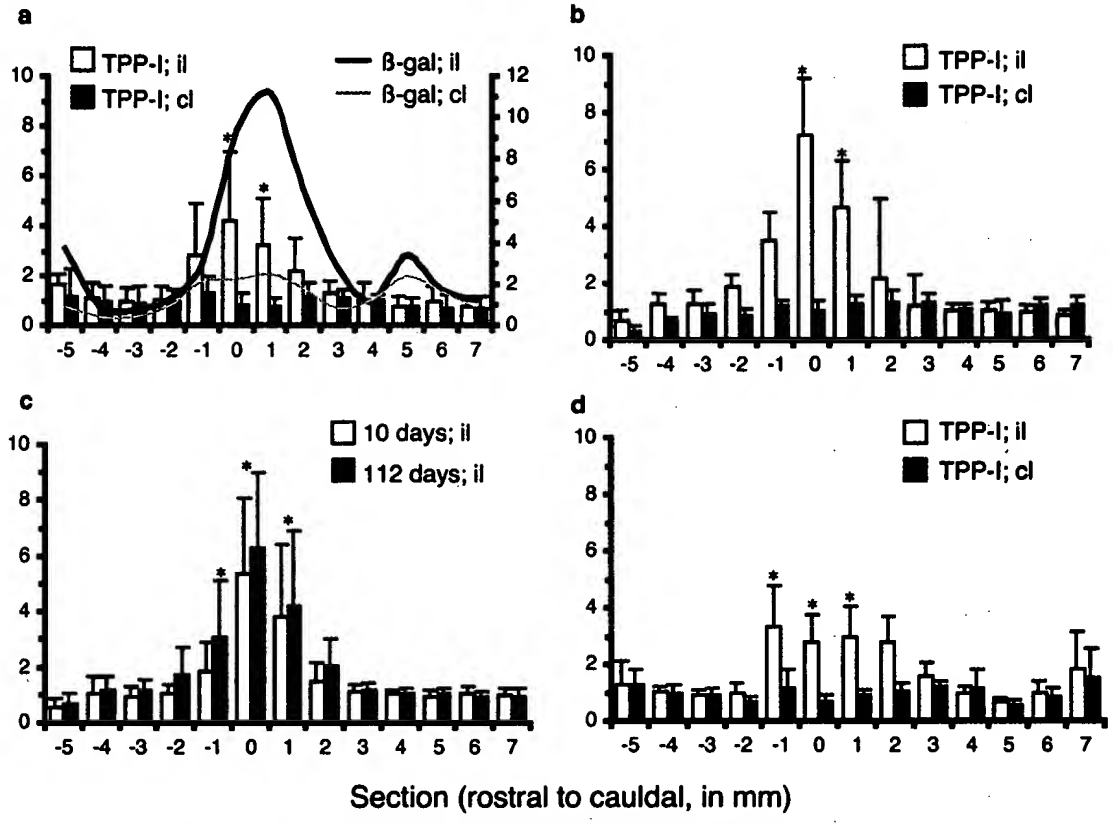

*Figure 5 TPP-I enzyme activity in brain lysates. The data are represented as fold increase in activity over non-injected controls for lysates harvested rostral (−5 mm) to caudal (7 mm) of the injection site (0 position). (a) Distribution of TPP-I and β-galactosidase 10 days after AdTTP-I/nlsβgal injection. TPP activity data are depicted as bar graphs (left y-axis, fluorescence units/mg protein). β-Galactosidase activity data are shown as line graphs (right y- axis, pg β-galactosidase/mg protein). Black line, injected (ipsilateral, il) hemisphere. Gray line, non-injected (contralateral, cl) hemisphere. (b) TPP-I activity 10 days after FIVTPP-I-mediated gene transfer. (c) Comparison of TPP-I activity in the injected hemispheres at 10 and 112 days following FIVTTP-1 gene transfer. (d) TPP-1 distribution 10 weeks after AAV5TPP-I injection into mice striata. Data represent the means ± standard deviation. In (b)–(d), y-axis is TPP-I activity (FU/mg protein). *$P \leq 0.05$ relative to control sections in all cases.*

following an intrastriatal injection (J Heth and BL Davidson, unpublished observations).

In addition to qualitative comparisons using immunohistochemistry, enzyme assays on brain lysates were done. Unlike IHC using the antibody described, endogenous levels of active TTP-I were detectable throughout the brain. At various time points after intrastriatal injection of recombinant Ad, AAV or FIV, 1-mm-thick coronal tissue slices from the entire brain were harvested and the coronal sections separated into injected (ipsilateral) and non-injected (contralateral) hemispheres. Enzyme activity in each hemisphere was independently assayed with and without pre-activation. TTP-I was in the active form as pretreatment at acidic pH did not increase levels of activity. Thus, secreted, inactive TPP-I is readily taken up and activated, or in contrast to our *in vitro* data, neural cells *in vivo* secrete TPP-I in the active form.

In mice receiving injections of 7×10^7 i.u. AdTPP-I/nlsβgal, TPP-I activity was up to six times higher than endogenous levels immediate to the injection site, and significantly above endogenous levels in the surrounding 4 mm ($P<0.05$ for 0 and 1 mm, respectively relative to Adβgal controls). The elevation in activity was limited to the injected hemisphere (Figure 5a). In general β-galactosidase activity correlated with TPP-I distribution, except for a consistent peak 5 mm caudal of the injection site.

FIVTPP-I injections (2.5×10^6 i.u.) also resulted in a similar-fold increase in TPP-I activity when compared to endogenous levels in control brain sections. At 10 days after injection, TTP-I activity was significantly higher than background within 2 mm of the injection site (Figure 5b; $P<0.05$ for 0 and 1 mm respectively, relative to control). By 16 weeks (112 days), the TPP-I activity was elevated relative to the 10 day time point, with a trend toward an increased rostral distribution (Figure 5c; $P<0.05$ for the −1, 0 and 1 mm sections, respectively relative to control). There was no further increase in enzyme levels or distribution in brains harvested and assayed 33 weeks after injection (data not shown).

Similar to AdTPP-I/nlsβgal and FIVTPP-I, AAV5TPP-I (5×10^9 pt) injections resulted in TPP-I enzyme activities five-fold over background. However, and unlike brains from FIVTTP-I injected mice, AAV5TPP-I did not result in a distinct peak of TPP-I activity. We found elevated, nearly equivalent levels of enzyme 4 mm around the injection site (Figure 5d) which was significantly greater

than control treated mice ($P<0.05$ for –1, 0 and 1 mm sections, respectively). Together, the data support that TPP-I can be expressed in brain following transduction of neurons, glia and ependyma, with spread of enzyme detectable up to 4 mm surrounding the injection site.

Discussion

Delivery of TPP-I to cells in the CNS by viral-mediated gene delivery may provide therapy for LINCL. Amelioration of the CNS deficits of this disorder would likely require widespread, rather than focal correction. Using other animal models of lysosomal storage disease as guides,[14,15,19,22] we hypothesize that TPP-I secretion from transduced cells, followed by subsequent uptake by non-transduced cells, would lead to an extensive area of recombinant enzyme activity. In the current study we found that TPP-I expressed in brain is secreted and active, and using IHC and enzyme assay found evidence of TPP-I 2–4 mm from the injection site. While the sensitivity of our assays precludes the detection of increased enzyme expression beyond this region, we believe that the spread of enzyme may extend beyond the 2–4 mm detected. The best assessment of the extent of enzyme spread and correction will come from studies performed in animals deficient in TPP-I.

Similar to earlier work with TPP-I harvested from baculovirus-infected Sf9 cells, or overexpressing COS cells,[9] TPP-I secreted from A549 cells was inactive. In both cases, the enzyme could be auto-activated *in vitro* at pH<4.5, or alternatively, following endocytosis by LINCL fibroblasts and lysosomal activation. Surprisingly, we did not find evidence of inactive enzyme in brains following viral-mediated gene transfer of TPP-I. Pre-activation of tissue lysates at low pH did not enhance TTP-I activity levels, and the kinetics of each reaction were linear over the entire assay, indicating that essentially all of the TPP-I in the brain was in the active form. Our *in vitro* data support that TPP-I was secreted as the inactive 66 kDa form *in vivo* followed by immediate uptake and activation.

We were surprised to find few transduced TTP-I$^+$/βgal$^-$ cells given our prior experience with β-glucuronidase, and data from other published reports. This may reflect distinct differences between TPP-I and the lysosomal enzymes α-*N*-acetylglucosaminidase, arylsulfatase A, and β-glucuronidase with respect to their ability to spread from the site of secretion. Alternatively, it could reflect the sensitivity of our enzyme activity assay method, or the polyclonal antibody. The best indication of TPP-I spread, either through retrograde transport or by distribution through the CSF, will come from TPP-I-knock-out mice with a measurable and/or histological phenotype where issues of clearance of pathology relative to enzyme activity levels can be addressed.

The vectors used in this study resulted in a three- to seven-fold increase over endogenous TPP-I activity following a single injection, and TPP-I distribution increased from 10 days to 16 weeks in mice injected with FIVTPP-I. In AAV5 and FIV, two vectors known to provide long-term expression, these levels were maintained until the end of the experiment at 10 and 33 weeks respectively. The levels of TPP-I activity required for therapeutic benefit are currently unknown. Using other lysosomal disorders as a benchmark, generally 1–5% normal enzymatic levels are sufficient for beneficial effects by enzyme replacement therapies.[23–25] Again, therapeutic levels of TPP-I that are undetectable by IHC or enzyme assay, may be sufficient for correction of the cellular phenotype, as seen in the mucopolysaccharidosis type VII mouse model.[13,16,26]

Increased β-galactosidase activity in the region 5 mm caudal to the injection site in AdTPP-I-injected mice did not result in detectable local increases in TPP-I activity (Figure 5a). These cells were presumably infected at their termini followed by retrograde transport of the vector, leading to increased β-galactosidase activity. Lack of detectable TTP-I in these same cells could be due to assay sensitivity limits. An alternative possibility is that TPP-I was made in these cells with most anterogradely transported back to the injection site.

Injection of adenovirus into the cerebellum gave the most convincing evidence of secretion and uptake of TPP-I. Cells of the choroid plexus were very positive for TPP-I immunoreactivity but displayed no detectable β-galactosidase activity. Interestingly, expression of TPP-I in Bergman glia did not lead to TPP-I immunoreactivity in Purkinje cells. This may indicate that either Bergman glia do not secrete TPP-I, or that the nearby Purkinje cell soma and its extensive dendritic tree do not efficiently endocytose TPP-I.

In summary, the total distribution of TPP-I is the product of the intrinsic ability of the vector to spread from the injection site and the subsequent spread of the secreted gene product. Optimization of the efficiency of TPP-I delivery will require the use of vectors that demonstrate wide distribution and long-term expression. In addition, modifications of the secreted proteins may be employed to increase their ability to spread throughout the parenchyma.[13] Maximizing distribution of the vectors or the specific gene product will facilitate effective therapies for LINCL and other lysosomal storage diseases.

Materials and methods

Viral constructs

An adenovirus encoding TPP-I in the E1 region was generated by sub-cloning the human TPP-I cDNA[12] into the pacAd5CMV plasmid. The resulting shuttle (Ad5CMVTPP-I) was recombined with pacAd5 9.2-100 in HEK 293 cells to produce recombinant adenovirus particles, AdTTP-I.[27] The second adenovirus used in this study contained a nuclear targeted lacZ (nlsβgal) sub-cloned into the E3 region in addition to TPP-I in E1. To generate this construct, the existing pacAd5 9.2-100 plasmid was modified to include a SwaI restriction site after deleting the E3 region.[13] DNA containing nlsβgal was cut from the plasmid pAdCMVnlsβgal with PmeI and SpeI and sub-cloned into the pAd5E3RSV recombination shuttle. Ad5E3RSVnlsβgal was cut with SfuI and Ad5 9.2-100SwaI with SwaI and recombined using methods described earlier.[13,28] The resulting plasmid pacAd5 9.2-100nlsβgal was then transfected with the Ad5CMVTPP-I shuttle in HEK 293 cells to make the dual-expressing virus Ad5TPP-I/nlsβgal.[27] Adenoviruses were purified by the University of Iowa Gene

Transfer Vector Core by CsCl gradient purification and titered by plaque assay on A549 and HEK 293 cells.

For FIV constructs, the TPP-I cDNA was cloned into the pVETLRSVmcs FIV genome plasmid.[29] The TPP-I-containing plasmid was combined with pCFIVΔorfΔvif and pCMV-G in a triple transfection in HT 1080 cells.[19,29] The medium was collected over a 4-day period, passed through a 0.45 μM filter and centrifuged at 7500 *g* to concentrate the retrovirus particles. The pellet was then resuspended in 1 mL lactose buffer (40 mg/ml lactose in PBS). Viral titers of FIVTPP-I were estimated by infecting A549 cells with serial dilutions of the viral stock followed by immunohistochemistry for TPP-I. FIV particles were generated in the University of Iowa Gene Transfer Vector Core.

Recombinant AAV5 vectors were produced by triple transfection of the TPP-I expression cassette, containing the native AAV5 ITR and the Rous Sarcoma virus long terminal repeat promoter, a plasmid containing AAV5 rep and cap, and a third plasmid containing helper function from adenovirus type 5. Recombinant AAV5TPP-I was purified as described previously and titered by quantitative PCR.[20,30,31] The viral titer was 1.0×10^{12} genome copies (particles)/ml. AAV5TPP-I was dialyzed against lactated Ringer's solution prior to injection.

Animals and injections

Six-week-old C57Bl/6 mice were purchased from Jackson Labs (Bar Harbor, ME, USA) and housed at the University of Iowa Animal Care Facility. The University of Iowa Animal Care and Use Committee approved all animal procedures. For striatal injections, mice were injected at coordinates 0.4 mm rostral, 2 mm lateral from the bregma, at a depth of 3 mm with 5 μl injections of one of the following viruses: 7.0×10^7 i.u. of AdTPP-I/nlsβgal (n=12), 2.5×10^6 i.u. of FIVTPP-I (n=14) or 5×10^9 pt of AAV5TPP-I (n=6). For cerebellar injections, 2 μl of virus containing 2.8×10^9 i.u. of AdTPP-I/nlsβgal (n=3) or 1×10^6 i.u. of FIVTPP-I (n=3) was injected into the anterior cerebellar lobe underlying the midline posterior occipital bone using a Hamilton syringe cemented with a glass micropipette tip.[20] Control animals either received no injection (n=4), or were injected with Ad5nlsβgal (n=4).

Tissue harvest and processing

All animals injected with adenovirus and FIV were evaluated 10 days after injection (n=6 each) and AAV5 animals at 10 weeks (n=5). Mice injected with FIV animals were also evaluated at 16 weeks (n=4) and 33 weeks (n=3).

For cryostat sections and immunohistochemistry, animals were perfused with 2% paraformaldehyde. Brains were removed and post-fixed 2 h in 2% paraformaldehyde, cryoprotected overnight in 30% sucrose, embedded in OCT and sectioned on a cryostat at 10 μm for subsequent immunostaining.

For enzyme assays, mice were euthanized and the brains removed, cut rostral to caudal at 1 mm intervals and hemispheres separated for analysis. Samples were frozen immediately in liquid N_2 and extracts prepared by homogenization in 500 μl of ice-cold lysis buffer (0.15 M NaCl, 0.1% Triton X-100). Nuclei and cellular debris were pelleted at 10 000 *g* at 4°C. The soluble fraction was removed and saved for TPP-I analysis. Nuclear pellets from Ad-injected mice were retained for β-galactosidase activity and were sonicated for 10 s in 500 μl of lysis solution. All samples were frozen at −80°C until assayed. Protein concentrations were determined by the DC protein assay (BioRad, Hercules, CA, USA).

TPP-I antibody and immunohistochemistry

Antibodies against TPP-I were generated by injecting rabbits with 500 μl of 1×10^{12} pt/ml of AdTPP-I into four intramuscular and one intradermal site. The rabbits were boosted with the same dosage and routes 2 weeks later. Serum aliquots were stored at−20°C. Rabbit serum was tested for TPP-I specific antibodies by immunostaining (1) transfected cells containing expression plasmids devoid of all adenovirus sequences, (2) cells infected with FIVTPP-I, and (3) tissue sections from mice injected with adenovirus expressing human β-glucuronidase and nuclear-targeted β-galactosidase (Adβgluc/nlsβgal). Antibodies directed against TPP-I were detected in TPP-I-expressing tissues and cells but not in Adβgluc/nlsβgal-injected mice. Rabbit anti-TPP-I serum was used at 1:600. To detect neurons, mouse anti-NeuN 1:100 (Chemicon International Inc., Temecula, CA, USA) directly conjugated to Alexa 568 (Molecular Probes, Eugene, OR, USA) was used. Polyclonal rabbit anti-β-galactosidase (BioDesign International, Sao, MN, USA), directly conjugated to Alexa 568 and diluted 1:1500 was used to detect cells infected with adenovirus. All antibodies were diluted in 3% BSA, 0.1% saponin, 0.3% Triton X-100 in PBS (diluent). After blocking tissue sections for 30 min in diluent containing 10% serum, samples were incubated with primary antibodies overnight at 4°C. Samples were washed extensively in diluent and stained with fluorescently labeled secondary antibodies for 2 h at room temperature. Photomicrographs were captured using Adobe Photoshop and a SPOT/RT digital camera (Diagnostic Inst, Sterling Heights, MI, USA) on a Leica DMRBE fluorescent microscope or Olympus IX70 inverted microscope.

LINCL fibroblasts

LINCL fibroblasts previously isolated from patients were kindly provided by Dr Peter Lobel (Rutgers University, Piscataway, NJ, USA). Compound heterozygous fibroblasts that contained a G3560C splice junction mutation and a C3674T non-sense mutation in *TPP-I* were used to evaluate the ability of these deficient cells to sequester and activate TPP-I expressed from viral vectors. Fibroblasts were grown in DMEM supplemented with 10% FCS plus pen/strep. Fibroblasts were cultured in media containing 2% FCS, DMEM and 10 MOI of AdTPP-I/nlsβgal added for 4 h, followed by removal of virus. Cells were cultured for an additional 48 h before TPP-I activity assays were done on media and cell lysate fractions. To test for TTP-I uptake, A549 cells were infected at an MOI of 50 in DMEM containing 2% FCS, DMEM for 4 h, followed by virus removal and an additional 48 h culture. The medium was removed 48 h after infection and added to patient fibroblast cultures in six-well plates. Media and cells were harvested and TPP-I activity measured. For immunohistochemistry, patient cells were cultured for 48 h in TPP-I-enriched media harvested from virally infected A549 cells and then stained with anti-TPP-I.

Enzyme activity assays

β-Galactosidase and TPP-I enzyme activities were analyzed in a 96-well fluorescence microplate reader (BMG Technologies, Durham, NC, USA) with Costar 3631 plates (Fisher Scientific, Pittsburgh, PA, USA). TPP-I activity was measured at 37°C using the substrate Ala–Ala–Phe 7-amido-4-methylcoumarin (AAF-AMC; Sigma St. Louis, MO, USA) at 380 nm excitation, 460 nm emission.[32] Prior to assay, samples were either maintained at neutral pH or pre-activated by incubation in citrate buffer (0.15 M NaCl, 0.05 M sodium citrate pH 4.2) for 20 min. Plates were pre-warmed to 37°C prior to the addition of substrate (50 µl of 400 µM AAF-AMC in citrate buffer). Samples were read every 2 min for 30 min. TPP-I activities from all mice were expressed as fluorescent units per minute per mg protein. Endogenous TTP-I activities from non-injected control mice were used to determine fold increase in expression after viral injections.

β-Galactosidase activities were measured in the nuclear fraction of all adenovirus-injected mice using the FluoReporter *lacZ* Quantitation Kit (Molecular Probes, Eugene, OR, USA) in accordance with the manufacturer's directions. Standard curves were generated using 0.02–5 ng purified β-galactosidase (Sigma, St. Louis, MO, USA). Aliquots of 5 µl of nuclear extract or β-galactosidase were incubated with 1.1 mM 3-carboxy-umbelliferyl β-D-galactopyranoside in reaction buffer (0.1 M sodium phosphate, pH 7.3, 1 mM magnesium chloride and 45 mM β-mercaptoethanol) for 30 min at room temperature. Stop buffer (0.2 M Na_2CO_3) was added and the fluorescent product measured at 380 nm excitation and 460 nm emission. Emission values were converted to pg β-galactosidase per mg protein based on β-galactosidase standard curves and sample protein concentrations.

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